American Journal of Obstetrics and Gynecology

VOL. 62 NOVEMBER, 1951 No. 5

Original Communications

STUDIES ON THE IRON DEFICIENCY ANEMIA OF PREGNANCY*

Including Plasma Volume, Total Hemoglobin, Erythrocyte Protoporphyrin in Treated and Untreated Normal and Anemic Patients†

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NEW and improved biochemical and biophysical methods have reopened the entire problem of the anemias of pregnancy. Several laboratories are actively engaged in such studies in iron deficiency.[1-7] Morphological techniques, including all types of hemoglobin and red cell measurement, are still, and will probably continue to be, the best clinical approach to the anemia problem. However, these disciplines reached their peak value years ago, as the excellent studies of Strauss and Castle[8] and others[9, 10] have revealed. The purpose of this paper is to show how the determinations of plasma volume and erythrocyte protoporphyrin augment routine hematological methods in the identification of iron deficiency and in the evaluation of response to therapy.

Methods and Materials

The patients studied were exclusively from the low-income group in the clinics and wards of Charity Hospital. Most of the patients (90 per cent) were Negro. New prenatal patients were screened at their initial visits by determination of capillary hemoglobin. The sample was obtained by pricking of the finger. From this preliminary survey patients were chosen for complete study.

All of the studies were done in the departmental research laboratory by one or the other of two technicians trained in hematological techniques. All blood pipettes were certified and retested by United States Bureau of Standards. With the exception of the screening test, all blood was drawn by venipuncture without stasis into a syringe moistened with heparin to prevent coagulation.

*Presented, by invitation, at the Seventy-fifth Anniversary Meeting of the American Gynecological Society in New York City, May 7 to 9, 1951.

†Aided in part by a grant from the White Laboratories, Inc.

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With few exceptions (routine blood counts only), all tests were done with the patient at rest and fasting. Hemoglobin was determined as oxyhemoglobin in the Evelyn photoelectric colorimeter and calibrated by the Van Slyke oxygen capacity method. Packed erythrocyte cell volume (P.C.V.) was done in the Wintrobe hematocrit and centrifuged for 30 minutes at 3,000 r.p.m. Sickling was determined by exposure of whole blood to CO_2 for 10 minutes.[11] Reticulocytes were identified by the brilliant cresyl blue stain.

Plasma volume was measured by the method of Gregersen[12] from a single venous sample drawn exactly 10 minutes after injection of T-1824. Repeated determinations within a short period of time[13] upon the same patient have established the validity of the method. Free erythrocyte protoporphyrin was determined upon the red blood cells by the method of Watson and Grinstein.[14]

Whenever indicated, quantitative serum bilirubin, urinary and fecal urobilinogen, and erythrocyte fragility were done. Serum iron and iron binding capacity were also determined from time to time. These tests were neither routinely nor consistently done and will not be reported.

Molybdenized ferrous sulfate* was used throughout the study. The dose was standardized at 0.39 Gm. (6 grains) three times daily with meals. The daily dose of ferrous sulfate was 1,170 mg., yielding 240 mg. of iron. The amount of molybdenum sesquioxide was 18 mg., yielding 15 mg. of molybdenum. For purposes of brevity the term iron therapy in the remainder of this report signifies that the above therapeutic routine was followed.

Results of Screening

Capillary hemoglobin of 4,015 patients was determined at the time of their first prenatal visits (Fig. 1). It is evident that many pregnant women in this area are anemic. Approximately 20 per cent of these women have hemoglobin levels below the absolute accepted minimum for normal pregnancy of 10 Gm. per cent. If the more accurate minimum of 11 Gm. per cent is used, 50 per cent of our patients are anemic. This is similar to the figure reported by Ferguson[15] in Mississippi and slightly higher than those reported by Traylor and Torpin in Georgia.[16]

Blood counts made from "finger prick" samples are notoriously inaccurate. They are also apparently lower than corresponding samples of venous blood. To test this difference comparisons of the two were made (Fig. 1). A rather constant difference of 0.5 Gm. per cent can be seen. As the capillary values are usually actually or spuriously lower than venous values, there was little danger of missing true anemia. On the basis of estimated values of venous blood the incidence of anemia in this group would be slightly less than calculated above.

Further study of these data showed that there was little difference between average values for primigravidas and multigravidas except late in pregnancy. At this time the primigravidas had somewhat lower values. Therefore, there is no evidence to suggest that repeated childbearing increased the incidence of anemia.

Results of Study

The patients for the study were obtained from those screened in clinic and a few others admitted directly to the hospital wards. All patients with severe anemia (hemoglobin less than 8 Gm. per cent) were studied. Many of those with moderate anemia were also studied (hemoglobin from 8 to 10 Gm. per cent). Only a few with mild anemia (hemoglobin 10 to 11.5 Gm. per cent in early pregnancy) were included. The magnitude of the task and the lack of cooperation by some patients made a study of all impossible.

*Mol-Iron, supplied by the White Laboratories.

The value of a study of this type is many times increased by serial chronological observations of each patient. For this reason no patient is included who did not report for continued study. Complete studies were done upon 66 patients during 402 outpatient examinations. The average was 6.1 visits per patient. No one was included who had fewer than 4 visits. Repeated examinations during a period of hospitalization, daily reticulocyte counts, etc., are not included in this calculation.

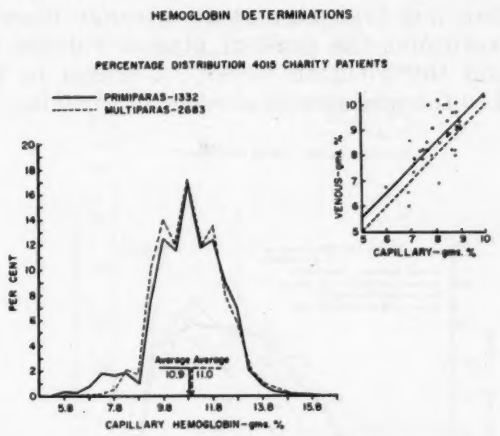

Fig. 1.—Shows the high incidence of anemia in charity patients based on the finger prick (capillary) blood. The upper right insert shows a comparison of capillary and venous blood. The latter ranges about 0.5 Gm. per cent higher.

On the basis of studies to be described, these patients were divided into two major categories, those who were normal and those who had iron deficiency anemia. Each of these were further subdivided on the basis of iron therapy.

I. Normal		
1. Controls untreated		14
2. Controls treated		7
II. Iron deficiency		
1. Anemia untreated		10
(Five had to be treated before delivery)		
2. Anemia treated		35
a. Those treated prior to thirty-second week	20	
b. Those treated after thirty-second week	15	
Total		66

At the beginning of the study there were 31 control patients and 35 patients under treatment. Five of the anemia controls became so severely anemic as to require therapy, making a final total of 40 treated patients. Satisfactory, but incomplete, data, which will be mentioned later, were obtained from 27 additional patients with iron deficiency anemia. Excluded from the study were patients with sickle-cell disease, Holly's refractory anemia of pregnancy,[1] Mediterranean anemia, and acute hemolytic anemia. Only two patients had megaloblastic (pernicious anemia) of pregnancy.

Plasma Volume.—A single isolated determination of plasma volume during pregnancy is utterly useless. By contrast periodic study of a patient gives useful information especially as regards changes in plasma volume. Under basal conditions we have measured plasma volume repeatedly within an hour to find surprising accuracy, ± 5 per cent. Fig. 2 shows the results obtained from 267 sequential studies of 66 patients. As variations between individuals

were great and variations within an individual were orderly it is advantageous to present the results as per cent change rather than absolute change in cubic centimeters of plasma volume. The curve is not unlike those of other investigators.[17-19] Without exception the plasma volume increased during pregnancy. The minimum individual increase was 14 per cent and the maximum increase was 121 per cent, while the average was 48 per cent. The exact peak of plasma volume is difficult to determine with present techniques. A sharply defined peak does not occur, for plasma volume is relatively high throughout the entire last trimester at an average increase of 40 to 50 per cent. With few exceptions the peak of plasma volume was passed between the thirty-second and thirty-eighth weeks. Changes in plasma volume were generally unrelated to the presence or absence of anemia.

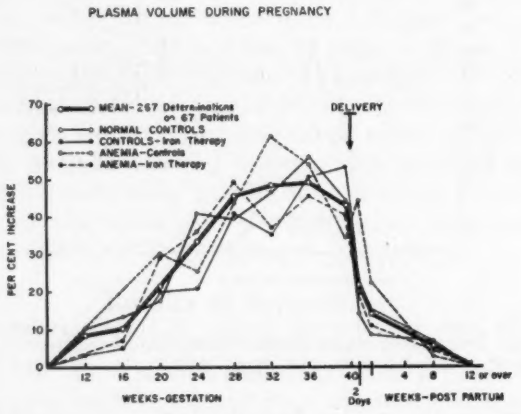

Fig. 2.—Significant increase in total plasma volume is present by mid-pregnancy, and it terminates in the high broad plateau of the last trimester with a small predelivery decline. The per cent increase of plasma volume is apparently unrelated to the presence or absence of anemia.

As the study progressed it was obvious that strange fluctuations of plasma volume occur during labor and immediately after delivery. Apparently, plasma volume rises markedly prior to delivery and then falls precipitously. Some of these changes have been described by Philpott.[20] For this reason all plasma volume determinations and all hematological surveys done during labor, delivery, and for 48 hours thereafter cannot be safely interpreted at present and therefore are not included in this paper. Detailed studies of these changes are under study at the present time and will be reported at a later date.

Total Hemoglobin.—It is generally conceded that the P.C.V. is the most accurate of the routine methods of hematological mensuration; the red blood cell count the least accurate. The hemoglobin in grams per 100 c.c. of blood lies somewhere between these two. The basic reliability of all these tests rests upon a stable plasma volume and under such conditions gives evidence of total hemoglobin mass.

During the second trimester of pregnancy the plasma volume increases on the average about 10 per cent per month with individual variations ranging from 3 to 25 per cent. Once known, this variable can and must be eliminated in a study of hemoglobin during pregnancy. The total hemoglobin in grams can be calculated indirectly when the plasma volume is known: Hemoglobin grams per 100 c.c. blood multiplied by total blood volume gives the total hemoglobin mass in grams. Such a calculation has been infrequently done

in the study of normal pregnancy,[7, 17] but in the evaluation of therapeutic response at times of rapidly changing plasma volumes it becomes essential.

Total hemoglobin mass increases progressively during normal pregnancy, reaching a maximum at term with an average increase of 15 per cent (Tables I and II). The increase is not evident prior to the twenty-fourth week of gestation and so lags behind the rapidly increasing plasma volume. Following delivery the total hemoglobin mass returns to its original normal level.

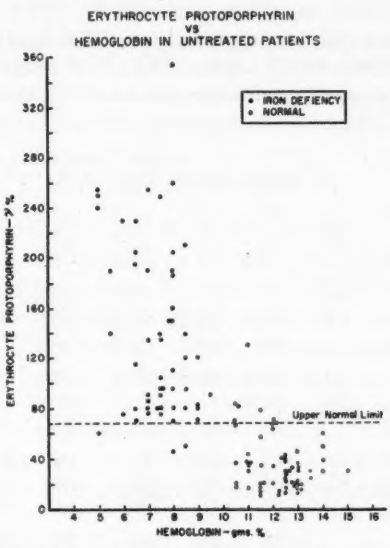

Fig. 3.—The erythrocyte protoporphyrin assists in the diagnosis of iron deficiency anemia as the anemic patients have elevated levels. It is possible that the normal controls with elevated E.P. may have a mild unrecognized iron deficiency.

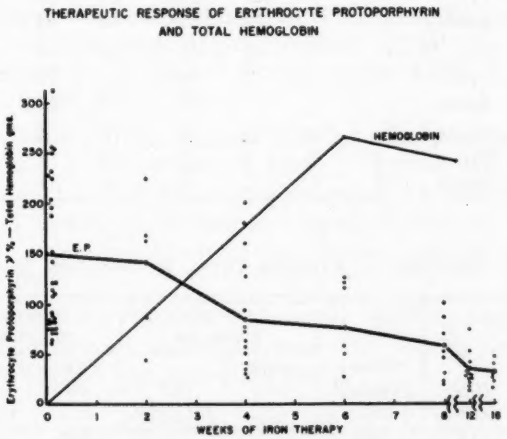

Fig. 4.—The erythrocyte protoporphyrin declines as the total hemoglobin increases. Although the E.P. falls to the upper normal levels within 6 weeks of therapy it continues to decline with continued therapy until the twelfth week. This suggests that the so-called upper normal limit of 60 gamma per cent may be too high.

Erythrocyte Protoporphyrin.—When globin is removed from hemoglobin a heme molecule remains which consists of iron bound to a porphyrin ring. The latter is closely related to bilirubin. Under normal conditions there is little free erythrocyte protoporphyrin (E.P.) as most of it is bound with iron.

During normal pregnancy the E.P. does not exceed 60 gamma per cent and is usually from 20 to 40 gamma per cent.[2, 3] If, however, there is a deficiency of iron more of the erythrocyte protoporphyrin remains free and increased amounts are found in the red blood cells. Only a few investigators have utilized this technique in the study of anemias of pregnancy. Holly[2] has shown that there is an elevation of the free erythrocyte protoporphyrin (E.P.) in patients with iron deficiency anemia of pregnancy.

TABLE I. CHANGES IN BLOOD COUNTS, ERYTHROCYTE PROTOPORPHYRIN, PLASMA VOLUME AND TOTAL HEMOGLOBIN DURING THE VARIOUS WEEKS OF PREGNANCY AND POST PARTUM

		WEEKS GESTATION								WEEKS POST PARTUM	
		12	16	20	24	28	32	36	40	1-2	8-16
Hgb. gm. %	Nor.	13	13	12.1	11.7	11.9	11	11	11.5	12	13.4
	Trt.	13	13	12.3	12.5	11.8	11.6	11.3	12.8	12.5	13.8
	Anem.		8.8	7.8	7.5	7.2	6.9	6.2	8.4	9.1	9.7
P.C.V., mm.	Nor.	40	39	37	35.5	35.2	34.2	34.4	35.7	38.4	41.1
	Trt.	35	39.3	38.2	38.3	36.5	37	36.7	38.4	38	41.6
	Anem.		28	28.5	27.1	26.4	25.4	24.2	31.5	32	37
M.C.H.C.	Nor.	32.6	33.5	32.8	33.2	33.8	32.5	32.2	32	32	32.5
	Trt.	33	33.2	33	32.2	32.5	32	32.2	32.8	32.7	33
	Anem.		31	28	27.1	26.1	27	26.4	26.5	28.5	28
M.C.V.	Nor.	97	92	92	94	94	93	92	93	91	93
	Trt.	91	96	95	91	95	95	93	94	88	94
	Anem.		80	78	76	81	77	80	84	83	84
Eryth. protop. (gamma) %	Nor.		33	38	30	46	43	43	69	44	31
	Trt.		20	18	27	34	36	28	28	24	24
	Anem.			140	137	143	147	197	168	105	92
Plasma vol. % increase	Nor.	14	14	18	41	39	47	56	44	12	-
	Trt.	3	5	20	21	41	35	50	53	15	-
	Anem.			30	25	43	61	55	34	22	-
Total hgb. % change	Nor.			-2	5	10	10	14	16	-	2
	Trt.			2	10	10	15	22	24	-	4
	Anem.				-12	-8	-13	-6	-5	-	6
Number patients	Nor.	3	8	9	6	6	7	7	8	9	13
	Trt.	1	5	5	5	6	4	7	7	6	7
	Anem.	1	1	2	4	6	6	4	4	4	5

TABLE II. CHANGES IN AVERAGE TOTAL HEMOGLOBIN MASS IN GRAMS

	NUMBER	INITIAL AVERAGE GM.	BEFORE THERAPY		BEFORE DELIVERY		POST PARTUM	
			AVERAGE GM.	%* CHANGE	AVERAGE GM.	%* CHANGE	AVERAGE GM.	%* CHANGE
Controls untreated	13	594			663	+15	612	+3
Controls treated	7	641	657	+2	793	+23	661	+1
Anemia untreated†	10	379			330	-13	391	+3
Anemia treated:								
Early Rx	19	327	330	0	566	+71	514	+57
Late Rx	17	348	334	-4	530	+59	589	+69

*The percentage changes are those from the immediately preceding column except the last which compares with the initial determination.

†Iron therapy in the treated control group was begun at or near the 20th week of gestation. Five of 10 anemia controls had to be removed from the study and treated by the 32nd week because of severely increasing anemia.

A study of the erythrocyte protoporphyrin was of value in two ways. First, in the detection of iron deficiency and, second, in the evaluation of therapeutic response. We found few patients with iron deficiency who failed to have some elevation of the E.P. Two hundred seventy-eight determinations were done upon 66 patients. Fig. 3 shows the relation of E.P. to hemoglobin in grams per cent. There is apparently no obvious correlation between the degree of anemia and the E.P. but the demarcation between the anemias and the normals is obvious. In the absence of a superimposed iron deficiency the patients with other types of anemia such as sickle-cell disease, Mediterranean anemia, and megaloblastic anemia had normal E.P. The response to therapy was reflected in the E.P. (Fig. 4). Most patients had normal levels after 8 weeks of iron therapy. The variations between individuals were great but studies of an individual showed progressive change.

Controls Untreated

Fourteen patients were used as normal controls. All entered pregnancy without evidence of iron deficiency. The average hemoglobin was 13 Gm. per cent and none was below 12 Gm. per cent (Table I).

During the course of gestation there was the customary fall of hemoglobin and P.C.V. without change in mean corpuscular hemoglobin concentration (M.C.H.C.). At the lowest point hemoglobin was reduced on the average to 11 Gm. per cent (12 per cent). Of interest was one patient (Fig. 6, *a*) who developed an iron deficiency (hypochromic microcytic) anemia while under study as a control. We learned that her dietary intake of iron was low but it was not altered. Note the apparent improvement in blood counts post partum.

The rise in plasma volume was high by the twenty-fourth week (+ 41 per cent) and reached a peak of + 56 per cent at the thirty-sixth week of gestation. One patient, A. H., showed a plasma volume increase of 93 per cent, at this time her hemoglobin was 9.1 Gm. per cent, yet the total hemoglobin mass had increased by 18 per cent. By coincidence in 8 of these 14 controls the normal nonpregnant plasma volume was approximately 2,500 c.c. At the peak of hypervolemia the respective plasma volumes were 3,250, 3,500, 3,550, 3,750, 3,760, 4,000, 4,600 and 5,000 c.c.

The rising total hemoglobin lagged behind the plasma volume from 2 to 4 weeks and reached a maximum at term. During the first two months after delivery the total hemoglobin mass dropped 14 per cent to the initial level. This postpartal hemoglobin loss averaged 86 Gm. or the equivalent of 700 c.c. whole blood. Yet the average estimated postpartal blood loss was only 260 c.c. per patient.

The erythrocyte protoporphyrin remained within upper normal limits except near term. The rise at this time was due chiefly to the rising levels of the patient who developed the iron deficiency.

Controls Treated

Seven patients in this group entered pregnancy without evidence of anemia. They continued with a generally adequate diet and in addition received supplementary molybdenized ferrous sulfate, 6 grains three times a day, during the last half of pregnancy.

The results paralleled those of the normal untreated controls (Tables I and II). P.C.V., R.B.C., and hemoglobin grams per cent declined, the latter 11 per cent without change in M.C.V. and M.C.H.C.

The plasma volume increased as did the total hemoglobin mass. The latter reached a maximum at term exhibiting an average increase of 24 per cent within a range of 15 to 66 per cent. The postpartal drop was again present. In this group the average was 134 Gm. of hemoglobin or the equivalent of 1,000 c.c. whole blood. Individual blood loss in this group never exceeded 300 c.c. yet at two months post partum the average total hemoglobin had fallen to within 1 per cent of the initial pretreatment level of early pregnancy.

The erythrocyte protoporphyrin remained normal with an average of 36 gamma per cent within a range of 10 to 48 gamma per cent. As individuals and as a group the E.P. was lower than in the normal controls.

One patient is of special interest (Fig. 5). On the basis of blood counts falling below normally accepted minimums, she might be classified as anemic while under therapy. Further study shows that the total hemoglobin mass at this time had increased 49 per cent but it was masked by a 94 per cent increase in plasma volume.

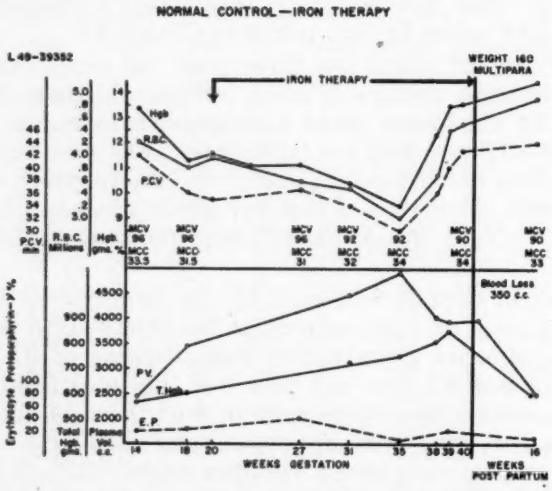

Fig. 5.—In spite of adequate diet and supplemental iron therapy the routine blood counts show development of an apparent anemia because of marked increase in plasma volume. Yet there is actually a marked increase in total hemoglobin mass and a normal erythrocyte protoporphyrin.

Anemia Controls

This group of 10 patients exhibited obvious iron deficiency by all of the laboratory methods at the time of the initial visit. No dietary instructions were given and no therapy was immediately begun. Tables I and II show the results. Every patient had a microcytic hypochromic anemia.

The total hemoglobin decreased progressively, reaching an average decline of 13 per cent between the thirty-second and thirty-sixth weeks. At this time five of the patients were so severely anemic as to require therapy. They will be included in the treated group. The remaining five, less severely anemic, continued through the study. For this reason the data (Table II) are not representative of the entire group after the thirty-second week of pregnancy.

The erythrocyte protoporphyrin was clearly elevated at the initial visit and continued to rise as the anemia progressed, reaching an average of 197 gamma per cent, range 75 to 253, prior to therapy or prior to delivery if untreated.

Anemias Treated

Time and expense were the chief limiting factors in the number of patients with iron deficiency anemias to be treated. Of the several hundred having anemia something less than 100 began the study. It was possible to study repeatedly and completely 39 of this group. An additional group of

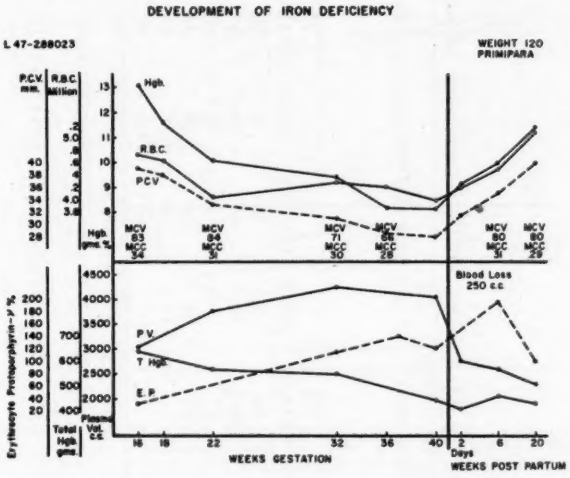

Fig. 6*a*.—All tests show a hypochromic microcytic iron deficiency in development. The postpartal decrease in plasma volume suggests an apparent improvement in blood counts but the falling total hemoglobin mass and high E.P. do not.

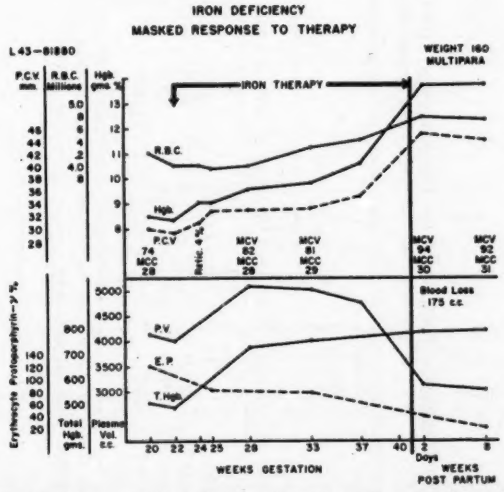

Fig. 6*b*.—During the first 6 weeks of iron therapy the red blood count was unchanged, the hemoglobin rose only 1 Gm. per cent and the P.C.V. 3 mm. This would appear to be a very poor response to iron therapy but at the same time the total hemoglobin increased 200 Gm., or the equivalent of 1,500 c.c. whole blood.

26 women had something less than complete study and will be mentioned later. The remainder were disinclined or unable to cooperate and had to be dropped from study. For purposes of presentation these patients have been divided into two groups, those treated before the peak of plasma volume was reached (about 32 to 34 weeks) and those treated after that time. The

TABLE III. COMPARISON OF RESPONSE OF HEMOGLOBIN (GRAMS PER CENT), P.C.V., AND TOTAL HEMOGLOBIN MASS (GRAMS) TO MOLYBDENIZED FERROUS SULFATE THERAPY

		BEFORE TREATMENT	1		2		3		4		6		OVER 6	
	TIME	MEAN	MEAN	% CHANGE	MEAN	% CHANGE	MEAN	% CHANGE	MEAN	% CHANGE	MEAN	% CHANGE	MEAN	% CHANGE
Hgb. gm. %	Early*	7.4	8.1	10	8.9	13	9.3	18	9.6	26	9.7	28	11.0	50
	Late†	7.1	7.8	11	9.0	20	9.3	24	10.0	36	10.6	47	-	-
P.C.V., mm.	Early*	26.6	27.7	5	30.3	9	31.3	17	32.5	19	32.7	22	36	27
	Late†	26.5	29.1	10	32.3	17	33.3	20	34	26	36	36	-	-
Total hgb. gm.	Early*	327			416	27			512	56	612	87		
	Late†	335			407	20			507	54	595	80		

*Treatment during the period of rising plasma volume was called early.
†Treatment thereafter was called late.

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reasons for this arbitrary division will become apparent. Twenty patients were in the former category and 21 in the latter, including 5 patients transferred from the anemia controls. Table III compares the average response related to weeks of therapy. Fig. 7 shows the total hemoglobin response of

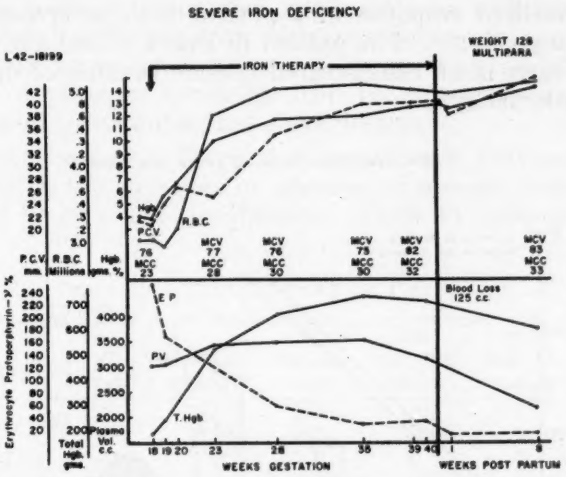

Fig. 6*c*.—An excellent therapeutic response by all criteria, note the relatively stable plasma volume. There was a postpartal loss of 100 Gm. of hemoglobin, the equivalent of approximately 800 c.c. of whole blood, yet the estimated blood loss was only 125 c.c.

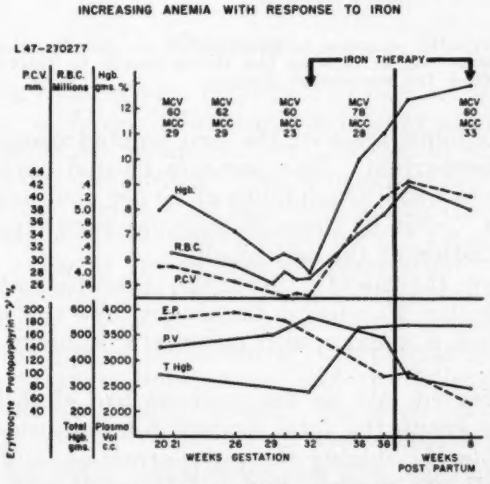

Fig. 6*d*.—This patient was an anemia control but increasing anemia necessitated therapy. Compare the exaggerated response as measured by routine blood counts with 6*b*. Note the similar increase in total hemoglobin mass.

each of the groups in grams, and the equivalent expressed in terms of whole blood. Six weeks of oral iron therapy will in the anemic mother produce the equivalent of 4 transfusions at a fraction ($\frac{1}{40}$) of the cost. If the therapeutic response of these two groups is judged by customary determinations of hemoglobin in grams per cent and P.C.V., then it appears that the better response occurs when the patient is treated late in pregnancy. For example, the 20 patients treated early produced 2.3 grams per cent of hemoglobin in 6 weeks while the 21 patients treated late produced 2.9 grams per cent in 4 weeks. If, however, the total hemoglobin mass is used for comparison it is obvious

that the rate of response of the two groups is essentially similar. When individuals are considered these masked responses can be great. Fig. 6, *b* shows a patient whose treatment began simultaneously with a rapidly increasing plasma volume. Six weeks of therapy produced but little improvement in blood counts but there was a 50 per cent increase in total hemoglobin. Fig. 6, *c* shows an excellent response in a patient with severe anemia and a relatively stable plasma volume. The patient in Fig. 6, *d* had a severe anemia which responded to therapy in an exaggerated fashion because of diminishing plasma volume late in pregnancy.

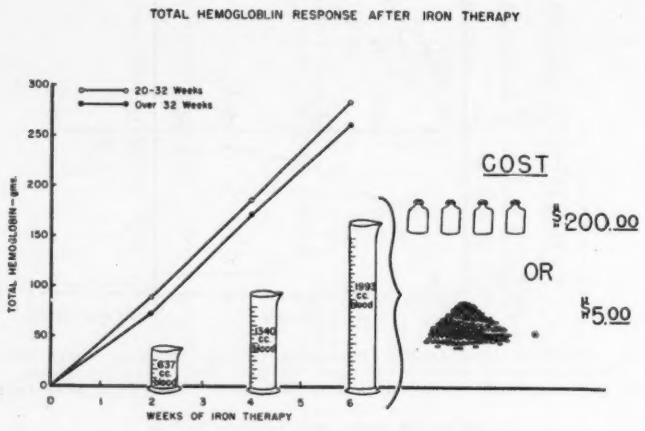

Fig. 7.—The therapeutic response is not related to the duration of pregnancy. If iron deficiency anemia is discovered at late as the thirty-fourth to thirty-sixth week of gestation there is still sufficient time for successful therapy.

The total hemoglobin mass of the two treated groups deviated considerably during the puerperium. The patients treated early showed an average postpartal decrease in total hemoglobin of 10 per cent yet all but two patients were fully "normal." Six of these 20 patients were treated during the puerperium without alteration of the end result.

There were two therapeutic failures. One patient showed incomplete response which was due to patient failure to take the medication regularly. The other occurred in a woman with polycystic kidneys and an atypical iron deficiency anemia.

The patients treated late on the average had slightly less than 4 weeks of therapy. In this group the total hemoglobin continued to rise, an average of 11 per cent (Table II), during the puerperium so long as therapy was continued. Sixteen patients treated during late pregnancy and the puerperium showed complete therapeutic response, while 5 patients who were treated during late pregnancy only had an incomplete final response. Every patient in this group responded to iron therapy.

The erythrocyte protoporphyrin dropped progressively in both groups regardless of delivery. It usually fell within the normal range following 6 to 8 weeks of iron therapy (Fig. 4). In every completely treated patient, with one exception, the E.P. was below 40 gamma per cent at the end of study. This patient had idiopathic asymptomatic porphyruria. Her erythrocyte protoporphyrin was 2,500 gamma per cent prior to therapy. It slowly fell to 307 gamma per cent under iron treatment long after the anemia had been corrected. In the 5 patients with incomplete response, and the one with no response, the E.P. remained above 60 gamma per cent.

In addition to the patients just described, 27 others were studied extensively but not completely. Of this group one patient who had iron deficiency anemia failed to respond to oral medication during pregnancy but made an excellent response when re-treated after pregnancy. Another patient was unable to continue therapy because of gastrointestinal distress. The remaining 25 patients responded apparently as well as those herein reported. From a total of 68 patients with iron deficiency anemia two patients (3 per cent) failed to respond to oral therapy with molybdenized ferrous sulfate. Of the 75 patients receiving iron therapy, one was forced to stop treatment because of gastrointestinal disturbances.

Maternal Complications.—There was no evidence that maternal complications were related to the presence or absence of anemia, however the groups were too small to be of much significance. Table IV summarizes the results.

TABLE IV. COMPLICATIONS OF PREGNANCY

	TOTAL	AVERAGE WEIGHT	BLOOD LOSS	PRE-MATURE LABOR	PRO-LONGED LABOR	TOX-EMIA	OTHER COMPLI-CATIONS
Controls untreated	24	134	200	0	1	2	2
Controls treated	7	145	175	0	1	2	1
Anemia untreated	10	116	150	0	0	3	2
Anemia treated							
Early Rx	20	115	180	1	0	2	7
Late Rx	16	111	175	2	0	3	3

Comment

Anemia is usually defined as a reduction of hemoglobin and/or red blood cells per unit volume of blood below some arbitrary standard. Such a definition implies that there is a compensatory increase in plasma volume as the total mass of hemoglobin diminishes. This is usually true within broad limits. Does anemia exist when there is an abnormal increase in plasma without a corresponding increase in total hemoglobin mass? Presumably not so long as there is sufficient capacity for oxygen transportation. Our studies as well as those of others[7, 17] have shown that there is a definite increase in total hemoglobin during pregnancy. Just as the stimulus for increased plasma volume is unknown so is the cause of increased erythropoiesis obscure. Our studies show that the bone marrow hyperplasia and the increased plasma volume precede the increasing hemoglobin mass. We were unable to correlate directly the increasing plasma volume with the increasing hemoglobin mass.

There seems to be little justification for the continued use of the term physiological anemia of pregnancy. In the first place, an anemia is pathological not physiological. Second, there can be no anemia in a normal pregnancy, only an apparent one. The term apparent anemia would describe those patients in whom hypervolemia masks the normal increase in total hemoglobin mass. Our studies would indicate that a hemoglobin level of less than 11.0 Gm. per cent after the twenty-eighth week of pregnancy suggests true anemia of pregnancy except in those patients with excessively high plasma volume.

Of interest was the definite increase in total hemoglobin mass exhibited by the normal controls who had supplementary iron. These results indicate that it is possible to drive upward the total hemoglobin in the absence of iron deficiency. It has been suggested that the uptake of iron by the pregnant woman is increased.[5] Once absorbed the iron may be used for the production

of erythrocytes. Is this a true need by the patient or does it represent another manifestation of food storage, apparently above basic needs, so characteristic of pregnancy? These data do not supply the answer.

Having produced this hemoglobin excess, in the absence of postpartum hemorrhage, the patient promptly loses it during the puerperium. This unaccountable loss of blood has also been reported by Philpott.[20] The mechanism, as yet unknown, may well be similar to that which occurs when the polycythemia of high altitudes disappears after the individual moves to low altitudes. Merino[21] suggests that two changes occur, the first an increased destruction of red cells and then a depression of the bone marrow activity. This problem is now under study. Whatever the reason or the method the pregnant woman by the eighth postpartal week has essentially the same hemoglobin mass as she did in early gestation.

Two factors have been largely responsible for the confusion concerning the value of oral iron therapy in anemias of pregnancy. Progressive changes in plasma volume varying from 14 to 121 per cent will be reflected directly in any study of routine blood counts. If it is rising, the response will be masked, if falling, the response will be exaggerated. The second factor is the problem of diagnosis. Modern biochemical methods will permit true identification of iron deficiency.

The major cause of anemias in pregnancy in the New Orleans area is iron deficiency. For every patient with megaloblastic (pernicious) anemia of pregnancy there are a hundred with iron deficiency. As a rule the anemia is present at the onset of pregnancy, but it can develop silently during pregnancy as Fig. 6, *a* shows. At least 90 to 95 per cent of these cases of iron deficiency anemia can be successfully treated with oral preparations of ferrous sulfate. Others have reported good results with such therapy.[22, 23] During late pregnancy we obtained an average response of 2.9 Gm. per cent of hemoglobin during 4 weeks of therapy. This is almost identical with the 2.8 Gm. per cent in 3.7 weeks following the use of intravenous iron as reported by Kartchner and Holmstrom[24] and others.[2, 25] In the severely anemic patient molybdenized ferrous sulfate will assist in the regeneration of 45 Gm. of hemoglobin per week or the equivalent of a 350 c.c. blood transfusion. From the excellent results herein obtained there is nothing to suggest that liver extract or related substances have any place alone or in combination with iron in the treatment of the iron deficiency anemia of pregnancy.

The results of this study suggest the following therapeutic plans. If the anemia is discovered during the first or second trimester, active treatment with iron will not only restore the normal amount of hemoglobin, but will also reproduce the normal increase in total hemoglobin. Treatment may be stopped at delivery. If the anemia is discovered during the last trimester, full normal response is not usually obtained before delivery; in such cases the treatment should continue for 6 or 8 weeks post partum.

Summary and Conclusions

1. A survey of 4,015 pregnant women from the clinics of Charity Hospital shows that half of them are anemic according to commonly accepted standards.

2. Newer biochemical techniques, including determination of blood volume and free erythrocyte protoporphyrin, in conjunction with routine hematologic mensuration, were used repeatedly throughout pregnancy in a controlled study of 66 normal and anemic patients.

3. Total plasma volume increased progressively, reaching a broad peak between the twenty-eighth and thirty-eighth weeks of gestation. Individuals maintained an orderly increase but variations between individuals were extreme, ranging from 14 to 121 per cent. This limits the usefulness of routine blood counts in any study of pregnancy anemias.

4. Calculation of total hemoglobin mass eliminates the influence of the unstable plasma volume and provides an excellent end point for evaluation.

5. The total hemoglobin mass increases progressively during apparently normal pregnancy, reaching a peak elevation of about 15 per cent at term. If these normal controls are treated with iron there appears to be an even greater increase in total hemoglobin. With or without therapy the total hemoglobin declines to the original level by the eighth week post partum.

6. With one exception, iron deficiency anemia was present at the time of the first prenatal visit. If untreated the anemia becomes more severe as pregnancy progresses.

7. Rapid or excessive change in plasma volume will mask or exaggerate the response to iron therapy when interpreted by routine blood counts. Calculation of total hemoglobin shows the true response. On this basis the oral administration of a molybdenum ferrous sulfate compound effectively treated 95 per cent of a group of 66 patients with iron deficiency anemia of pregnancy.

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Discussion

DR. FRANK E. WHITACRE, Memphis, Tenn.—Dr. Lund is to be congratulated on the completeness of this extensive study. That it involved an enormous amount of work is obvious. Studies on hemoglobin and its fractions are particularly difficult and time consuming. His studies on erythrocyte protoporphyrin have confirmed in pregnancy what was already known outside of pregnancy, but is a definite contribution. Since protoporphyrin has a strong affinity for combining with iron, it is to be expected that as iron deficiency anemia progressed, the erythrocyte protoporphyrin levels increased. The converse was also true, that in the treated anemic patients this same level gradually fell in proportion to the treatment with iron.

Several years ago, in considering our anemic patients, I was surprised to find that average levels of blood studies in pregnancy had not been done in our area of the country—at least to my knowledge. It seemed necessary to establish a base line for comparison, and this was done under the supervision of a competent hematologist. No patients were included who had known bleeding tendencies, and all patients studied were from the John Gaston Hospital charity service.

A group of 200 nonpregnant Negro women showed the following:

	R. B. C.	GRAMS HEMOGLOBIN
Highest	5,920,000	14.8
Lowest	3,260,000	6.5
Average	4,430,000	11.4

Of this series, 25.5 per cent had a red blood count of 4 million or less.

A group of 200 pregnant Negro women showed the following:

	R. B. C.	GRAMS HEMOGLOBIN	GRAMS PLASMA PROTEIN
Highest	5,580,000	14.5	8.6
Lowest	2,500,000	8.5	5.5
Average	4,140,000	11.2	6.8

Volume of packed red cells:	Highest	38.5%
	Lowest	23.0%
	Average	32.4%

R.B.C. of 4 million or less	37.5%
Hb. of 11 Gm. or less	45.0%
Anemic patients, fifth, sixth, or seventh month	70.0%
Toxemia of pregnancy	14.0%

In a study of 100 pregnant white woman, the following findings were recorded:

	R. B. C.	GRAMS HEMOGLOBIN	GRAMS PLASMA PROTEIN
Highest	5,600,000	14.5	7.6
Lowest	2,860,000	7.8	5.5
Average	4,180,000	11.6	6.5

Volume of packed red cells:	Highest	39.6%
	Lowest	24.4%
	Average	33.8%

R.B.C. of 4 million or less	55.0%
Hb. of 11 Gm. or less	22.0%
Toxemia of pregnancy	4.0%

Arbitrarily patients with 11 Gm. or less of hemoglobin were considered to be anemic.

The emphasis was in the study of the Negro patients, as they comprise 85 per cent of our total material.

It will be noted that the plasma proteins were included in both of the groups of pregnant women and this was to see if there was any correlation of low plasma proteins to our large volume of toxemic patients. There was no significant correlation.

In the two groups of pregnant patients, the average findings are all only slightly less for Negro than for white.

Our facilities at this time in Memphis would not permit a study of the magnitude of Dr. Lund's. It is probable that erythrocyte protoporphyrin determinations are too complicated for general adoption and that we can get reasonably accurate information on our patients from the hemoglobin and hematocrit determinations. The latter has an error of only 2 to 4 per cent.

Dr. Lund's extensive study may be of considerable value in the future. It emphasizes that the generally accepted standards for the results of blood determinations in one section of the country cannot be accepted as a normal or average level for the populace in another section, and that each region must determine its own average findings, in order to have an accurate base line upon which to determine what is abnormal for their area.

DR. E. L. KING, New Orleans, La.—I would like to ask Dr. Lund if he has had experience with intravenous iron in his cases?

DR HOWARD C. TAYLOR, New York, N. Y.—Does Dr. Lund imply that when we are evaluating our patients determination of plasma volume must now become a part of our clinical procedure?

DR. LUND (Closing).—I would like to thank Dr. Whitacre for his remarks. It is plain to see that we are dealing with similar types of material. The so-called pernicious (megaloblastic) anemia of pregnancy is exceedingly rare in our area. From these 4,000 patients there were but two with such an anemia of pregnancy. The remainder of the anemias not herein reported were sickle-cell disease, hemolytic anemia, or others, but the overwhelming problem in our area is iron deficiency.

Dr. King asked about intravenous iron. We have had little experience with it. Very few patients failed to respond to the oral administration of iron during pregnancy; in such patients intravenous iron may be of value.

Dr. Taylor has asked, must we do plasma volumes on every patient as we would do a blood count? It is a technique that is fairly accurate and not too difficult to do when the occasion arises, but, as we have pointed out, is of little value unless serial observations are made. The M.C.H.C. is probably the best of the simple guides to the discovery of iron deficiency.

UTERINE ACTION, NORMAL AND ABNORMAL*

WILLIAM C. W. NIXON, M.D. (LONDON), F.R.C.S. (ENGLAND), F.R.C.O.G.,
LONDON, ENGLAND

I HAVE chosen as my theme the action of the uterus since it is fundamental for the act of parturition. This subject, which has been studied over the centuries, has become during the last quinquennium the focus of much attention on the part of investigators in the United States and other countries. Uterine action is usually a coordinated affair but when it becomes incoordinate then tragedy awaits both mother and baby. Disordered uterine action (in the absence of mechanical obstruction) is one of the most pressing problems in the act of birth awaiting solution. It is obvious that the physiological intricacies of uterine action need first to be appreciated.

Pattern of Uterine Contractions

There has been considerable speculation as to the nature and pattern of uterine contractility. Bourne and Burn[1] inserted a balloon into the human uterus during labor and recorded the effect of drugs (pituitary extracts and ergot alkaloids). Ivy, Hartman, and Koff[2] attached balloons to a catheter which was introduced into the uterus of a monkey immediately post partum. Through an abdominal incision they were able to observe directly the activity of the uterus and cervix. They noticed a pattern of contractions starting from "nodes" near the insertion of the tubes. They also recorded the effect of such drugs as Pituitrin, Adrenalin, and ergotamine, and found that the cervix sphincter contracted under the influence of posterior pituitary. These investigations are fundamental and are of special interest to those of us who are studying the activity of the cervix in human pregnancy.

Malpas[3] has shown that a pattern of contractility develops when the muscu lature of the intact uterus of the pregnant woman is cut off from the central nervous system by spinal anesthesia. His observations were made upon pregnant women undergoing abdominal hysterotomy early in pregnancy or at the time of cesarean section late in pregnancy or in labor. Up to the twentieth week contractions started at what appeared to be a "node" at the uterine end of each Fallopian tube. This confirms in the human being the findings in the monkey of Ivy and associates above. Late in pregnancy and also in labor, Malpas noticed a mass contraction in which all parts of the myometrium appeared to contract simultaneously. He concluded that the normal motor action of the central nervous system on the pregnant uterus was inhibitory and sustained, not intermittent. Possibly some cases of abortion may be due to sudden suspension of this nervous inhibition.

Innervation of the Uterus

In a world of chaos the subject of innervation of the human uterus takes a high place. Authoritative opinion is so divided that it is difficult to know what to accept as much evidence has been based on animal experiment. Dr. J. Joseph[4]

*The First Solomon Theron DeLee Lecture delivered, by invitation, at the Chicago Lying-in Hospital, Oct. 27, 1950.

of the Anatomical Department of University College, London, has tried to bring order out of this chaos. After a wide perusal of the literature he has reached the following conclusions:

1. There is an efferent nerve supply of the uterus and the parts of the uterus which can be influenced by these nerves are the muscle, blood vessels, and the endometrium including glands.

2. There is an afferent nerve supply of the uterus.

3. Anatomical studies make it fairly clear that different parts of the uterus have different nerve supplies—fundus, body, cornua, lower uterine segment, cervix.

4. It is very misleading to draw conclusions about the nervous system of the human uterus and its functions from animal experiments because in different states, for example, the pregnant and nonpregnant, the uterus of any one animal may react differently to the same stimulus or drug. There are considerable differences between the reactions of different animals (species difference) to the same experiment.

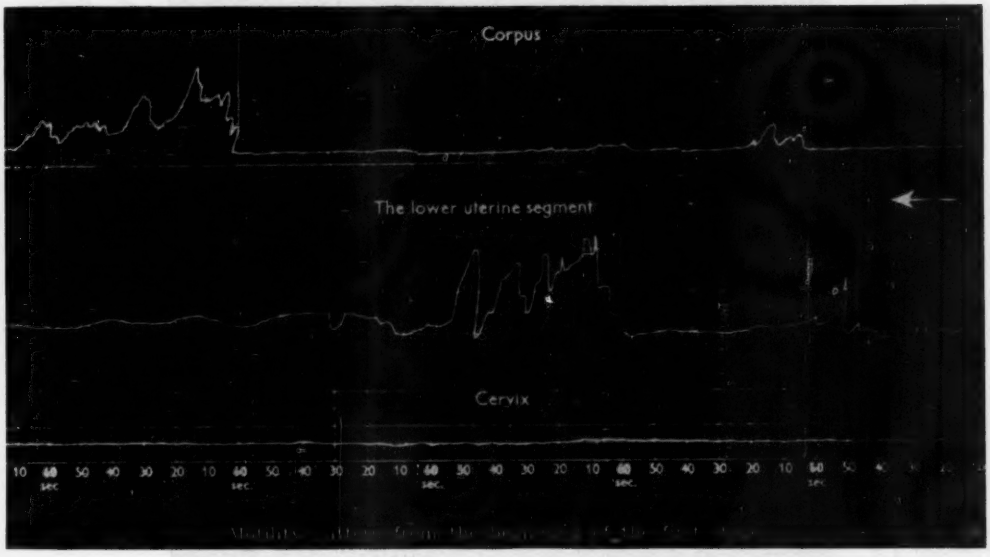

Fig. 1.—Incoordination of uterine contractions early in the first stage of labor.

Methods of Recording Uterine Activity

Lately there has been considerable development of methods for studying human uterine contractions both in pregnancy and labor (Dodek, Karlson, Lorand, Moir, Murphy, Reynolds, Woodbury). This subject has been fully reviewed by Harris and Gillespie[5] and by Reynolds[6] in his monumental work, "Physiology of the Uterus." Again, the recent study by Alvarez and Caldeyro[7] adds still more to our knowledge of contractility of the human uterus. Most of these studies have been by external hysterography which records activity of the corpus but not the cervix. Karlson[8] has devised an apparatus so that with electrical pressure receptors placed within the cavity, lower segment, and cervix, variations in pressure can be recorded simultaneously. He has obtained tracings from these regions of the uterus during different stages of labor.

Fig. 1 shows the motility pattern early in the first stage. There is incoordination between the various regions, each contracting independently.

With establishment of a peristaltic wave of contractions, dilatation of the cervix proceeds smoothly. Relaxation of lower parts when corpus contracts can be seen (Fig. 2).

These figures reveal pressure waves emanating from the cervix and due to contractions of the cervix itself and not to pressures transmitted from the cavity of the uterus. Our experiments confirm these observations and show that the cervix has the ability to contract, at times quite independently from the corpus. Karlson concluded that dilatation of the cervix depended on the establishment of a peristaltic pattern. The less that contractions of the cervix were isolated from or actually synchronous with those of other parts of the uterus, the more rapid was cervical dilatation.

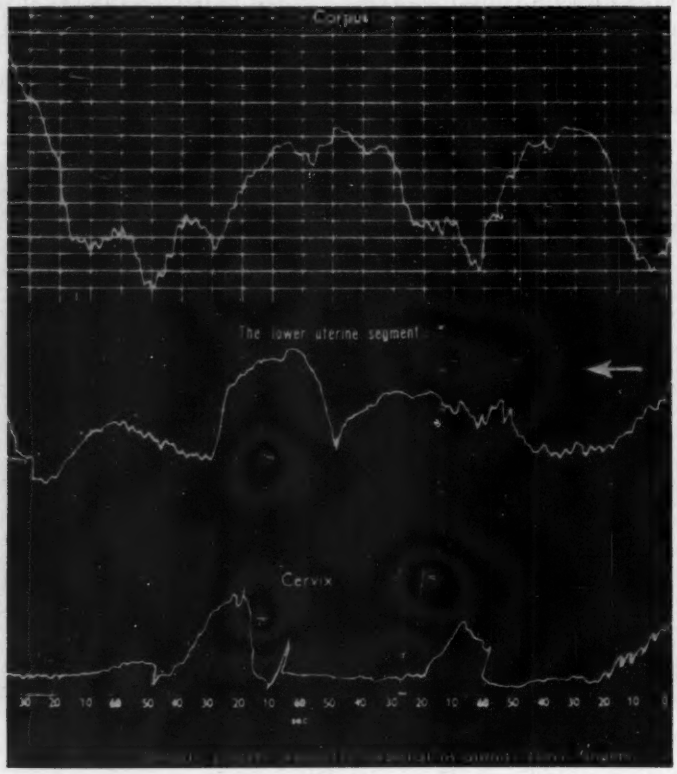

Fig. 2.—Peristaltic wave of contractions.

Chemical Aspects of Uterine Muscular Contraction

Needham[9] and other biochemists place adenosine triphosphate (ATP) in the center of the picture as the essential fuel. Szent Györgi[10] and his collaborators have succeeded in extracting two proteins, actin and myosin, from muscle. Neither of these is contractile but they combine to form a new substance, actomyosin, which under certain conditions in the presence of ATP becomes contractile.

The application of this newer knowledge to the human uterus has been studied by Naeslund and associates[11] at Upsala University. They have demonstrated that the distribution of actomyosin varies in different parts of the human uterus. Their findings are distinctly relevant to clinical obstetrics for they have shown that (1) even in the nonpregnant uterus the contractility of

the muscle of the corpus is greater than that of the cervix, (2) during pregnancy, actomyosin content is considerably increased, especially in the muscle of the corpus, and (3) during labor the content of actomyosin in the corpus is much higher and its ability to contract much greater than in the cervix. Again, it seems the uterus possesses a water-soluble compound (x-factor) which can stimulate the contractility of actomyosin. This factor is an enzyme and occurs only in uterine muscle. Needham, though not specifying the type and origin of the muscle, believes that leakage out of potassium ions which accompanies contraction (apparently due to setting free of potassium from some indiffusible combination) may have important effects on enzyme activity and protein structure.

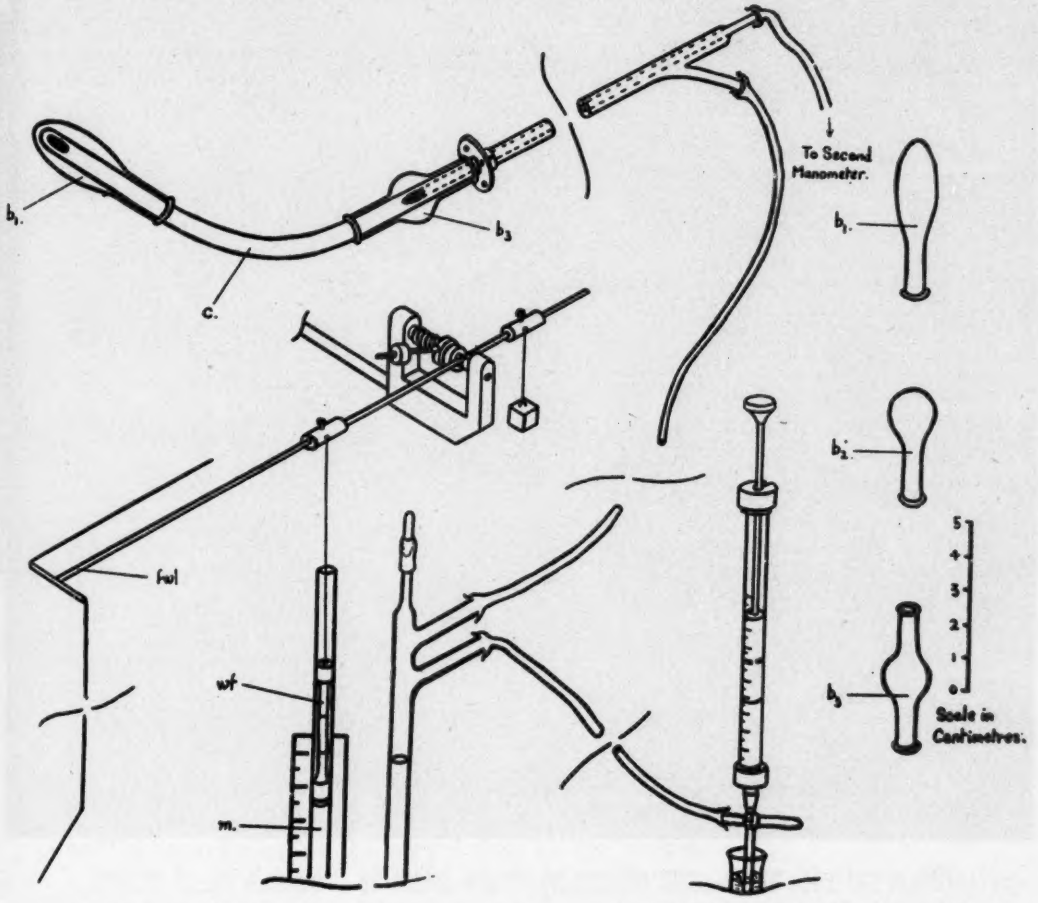

Fig. 3.—Metal catheter (c) for recording concurrently movements of the cervix and corpus; b 1, b 2, corpus balloons; b 3, cervix balloon. Balloons are filled with water and pressures transmitted to mercury manometers (m). Linearly magnified records are obtained by means of weighted floats (w f) and frontal writing levers (f w l).

Here on this frontier of research we see the harvest that results from cooperation between the biochemist and obstetrician, using the machinery of modern science.

Activity of the Human Cervix and Corpus Uteri in Early Pregnancy and Their Response to Drugs

At University College Hospital, Dr. H. O. Schild, of the Department of Pharmacology, University College, and R. J. Fitzpatrick, of the Veterinary

Laboratory of the Ministry of Agriculture, have collaborated in a study of the activity of the cervix and corpus of the human uterus and their response to drugs. External recording methods are not suitable for this purpose since they do not register the movements of the cervix. We have, therefore, used a method by which intrauterine and intracervical pressures could be recorded concurrently.

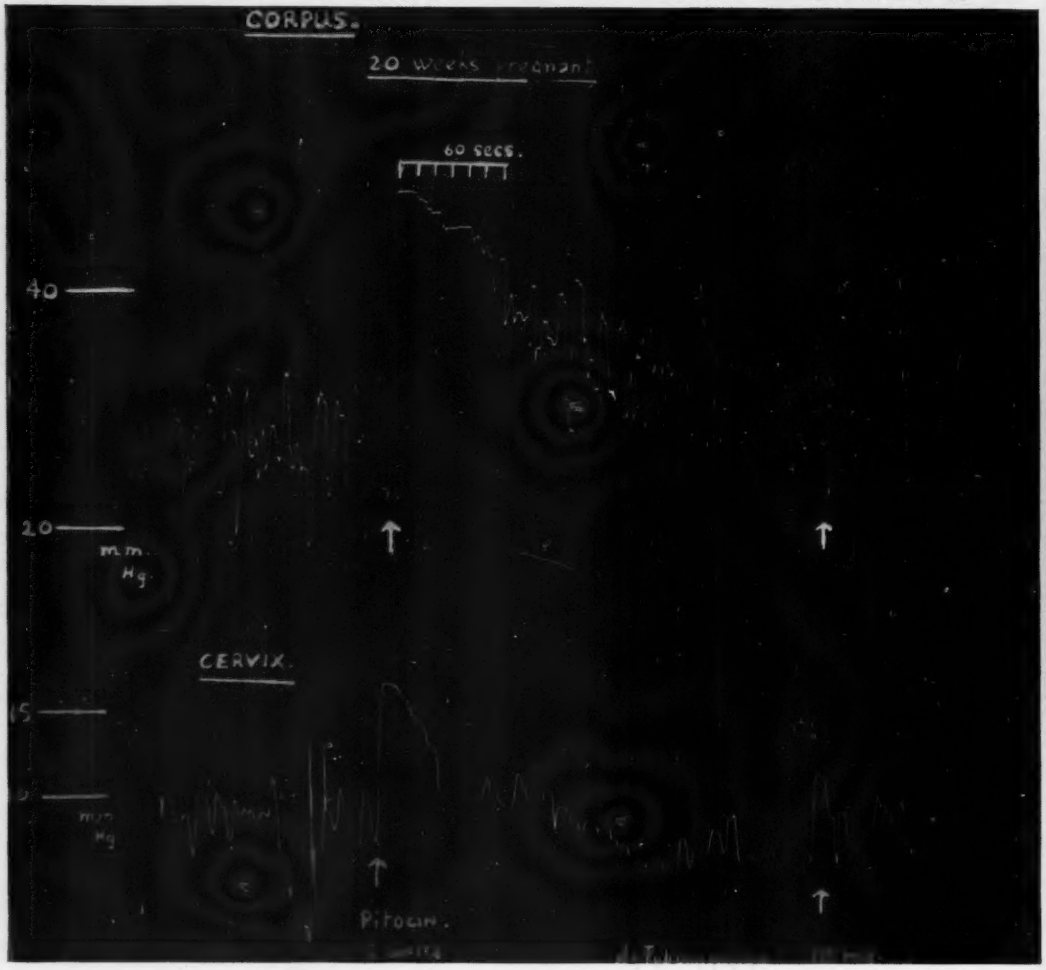

Fig. 4.—At 20 weeks: contractions of cervix following closely those of corpus.

During the course of hysterotomy either in the first or second trimesters of pregnancy records were obtained by means of a specially constructed catheter (Fig. 3) with balloons attached, so that movements of the cervix and corpus could be registered simultaneously. Occasionally a triple catheter was used so that balloons were in contact with three different regions of the uterus. It was often possible to obtain records before the patients were anesthetized and although at times the intrauterine pressure rose to over 50 mm. Hg when contractions were induced by oxytocic drugs, yet the patients did not complain of pain. Care was taken to ensure that the cervical balloon was within the cervical canal below the os internum but not protruding at the os externum, even where severe laceration had destroyed a great part of the vaginal cervix. The balloons

and the connecting system were filled with water and the pressure changes transmitted to mercury manometers, the movements of which were conducted by weighted floats to frontal or sideways writing levers recording on a moving drum.

Contractility of the Cervix

At times spontaneous contractions of the cervix were recorded but contractions were more usual after administration of drugs, particularly those of the ergometrine group. There was not a constant relationship between the activity of the cervix and the corpus; sometimes this was synchronous, at others it was independent.

Fig. 5.—At 20 weeks: cervical contractions, induced by intravenous ergometrine (0.25 mg.) have greater amplitude than the corpus contractions with which they are not in phase.

Fig. 4 is an example of cervical contractions following closely those of the corpus in a patient 20 weeks pregnant. After an intravenous injection of oxytocin (2 units) there was a powerful contraction of both corpus and cervix. Fig. 5 shows more clearly that contractions of the cervical balloon do not occur at the same time as those of the corpus and are not caused by mechanical transmission of pressure from above. An injection of ergometrine caused a more powerful contraction of the cervix than of the corpus.

Fig. 6 is an example of complete dissociation of corpus and cervix activity. The cervix in this case exhibited bouts of activity unrelated to the corpus.

The Action of Ergometrine and Methylergometrine

The effect of drugs of the ergometrine group can be seen in Figs. 5 and 7. In both these cases the cervix was mainly stimulated but in others the corpus was also stimulated by ergometrine. Within one or two minutes of intravenous injection of ergometrine the contractions of the cervix can be seen. These contractions are shallow and rarely exceed 10 mm. Hg in amplitude and in no case have they amounted to a tonic contraction of the cervix. Fig. 7 shows the effect of methylergometrine and Pitocin in the same patient. The former drug initiated activity in the cervix while the latter induced a powerful contraction

of the corpus without apparent action on the cervix. These experiments seem to show clearly that the contractions of the human cervix in early pregnancy may be influenced by drugs and that ergometrine acts mainly on the cervix and oxytocin on the corpus.

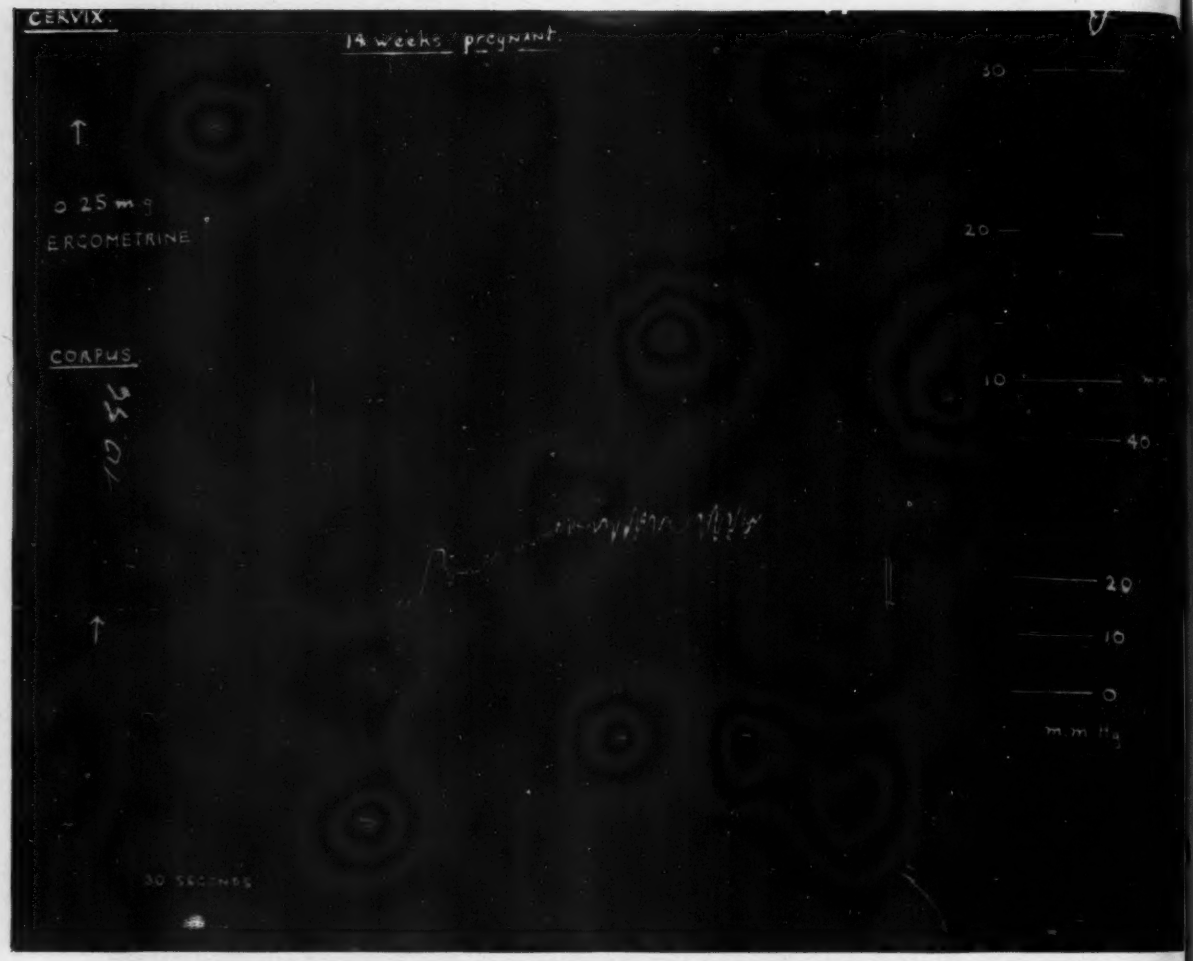

Fig. 6.—At 14 weeks: complete dissociation of activity of corpus and cervix.

The Action of Oxytocin

Oxytocin acted consistently on the corpus even in very early pregnancy. The effect on the cervix was variable; sometimes the cervix contracted, at other times it failed to respond or even, apparently, relax. Fig. 7 shows an abrupt rise of intrauterine pressure caused by oxytocin with the cervix unaffected. Earlier in this same experiment ergometrine had contracted the cervix without any obvious effect on the corpus. Fig. 8 illustrates the third type of reaction, namely, an apparent relaxation of the cervix. A triple catheter was used and three times in succession an intravenous injection of oxytocin caused a rise of pressure in both intrauterine balloons and a fall in the cervical balloon. Fig. 9 indicates that a rise of pressure was caused in both corpus and cervix by vasopressin while oxytocin produced a rise in the corpus but a small and definite fall in the

cervix. Seven times in three different patients a rise of pressure within the corpus and a fall within the cervix were noted, after oxytocin.

From these records it seems clear that the muscle in the cervix, unlike that in the corpus, frequently fails to contract in response to oxytocin.

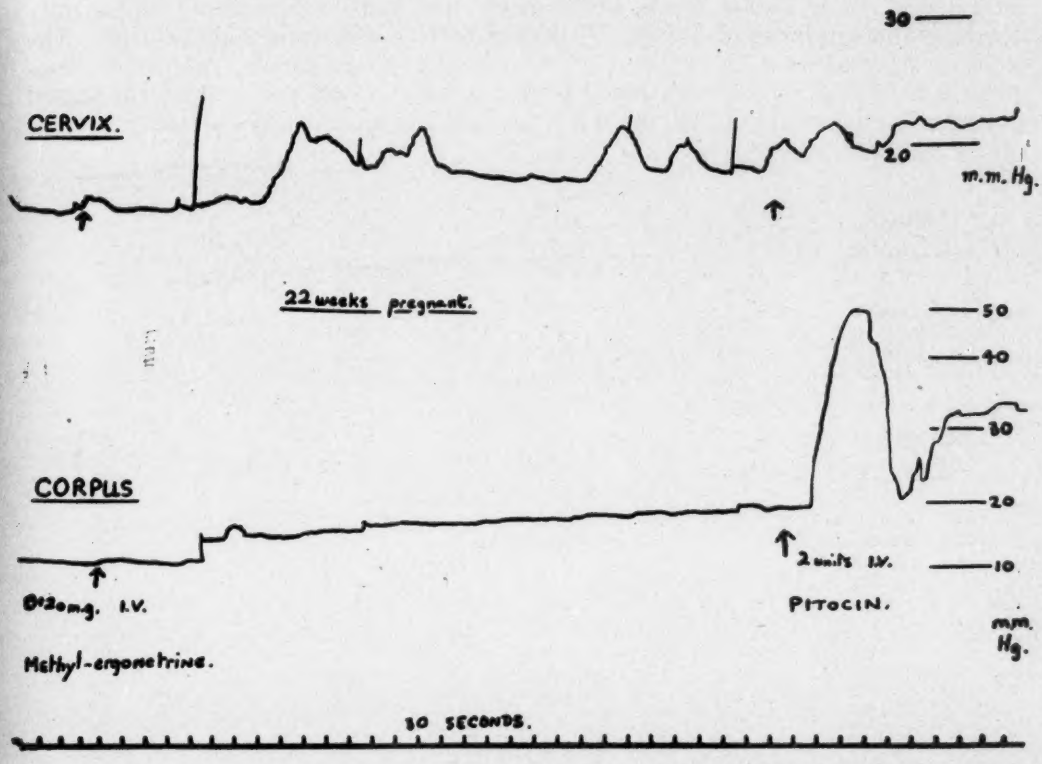

Fig. 7.—At 22 weeks: intravenous methylergometrine (0.2 mg.) causes contractions of cervix only, whereas intravenous oxytocin (Pitocin 2 u.) causes contractions of corpus.

Fig. 9 shows that an intravenous injection of oxytocin causes a sharp though transient fall of blood pressure, while vasopressin causes the well-known rise of blood pressure. A fall of blood pressure by oxytocin in men has previously been described by Woodbury and collaborators.[12] It occurred in both our anesthetized and unanesthetized patients, and could usually be detected if the blood pressure readings were taken immediately after injection. No subjective symptoms have been noted in the conscious patient. The fall of blood pressure was not caused by a contamination of histamine since the samples of oxytocin used contained less than 0.001 μg. histamine per unit as tested on the guinea pig's ileum.

Comparison of Activity of Oxytocin and Vasopressin

A series of observations was recorded to show the comparison of activity between vasopressin and oxytocin. Each series comprised three cases in which different doses were given to patients of approximately the same stage of pregnancy. In the first series, at approximately the eighth week, vasopressin was more than half as active as oxytocin, less than twice as active, and probably slightly less than equiactive. Similarly, in the second series at the sixteenth week, vasopressin was more than equiactive, less than twice as active, and more

than 1.5 times as active as oxytocin. Thus oxytocin appears about as active as vasopressin in early pregnancy but vasopressin is more active in the second trimester. This does not entirely confirm Moir's[13] finding that in early pregnancy vasopressin was more active unit for unit than oxytocin. (The samples of oxytocin and vasopressin used in these experiments were provided by Dr. Stanley White of Parke, Davis & Company, and were standardized biologically through the kindness of Dr. G. F. Stuart of the Wellcome Laboratories. The activities found were 96 per cent of the stated activity for the sample of vasopressin as tested by the rat's blood pressure test, and 94 per cent of the stated activity for the sample of oxytocin as tested on the guinea pig's uterus.)

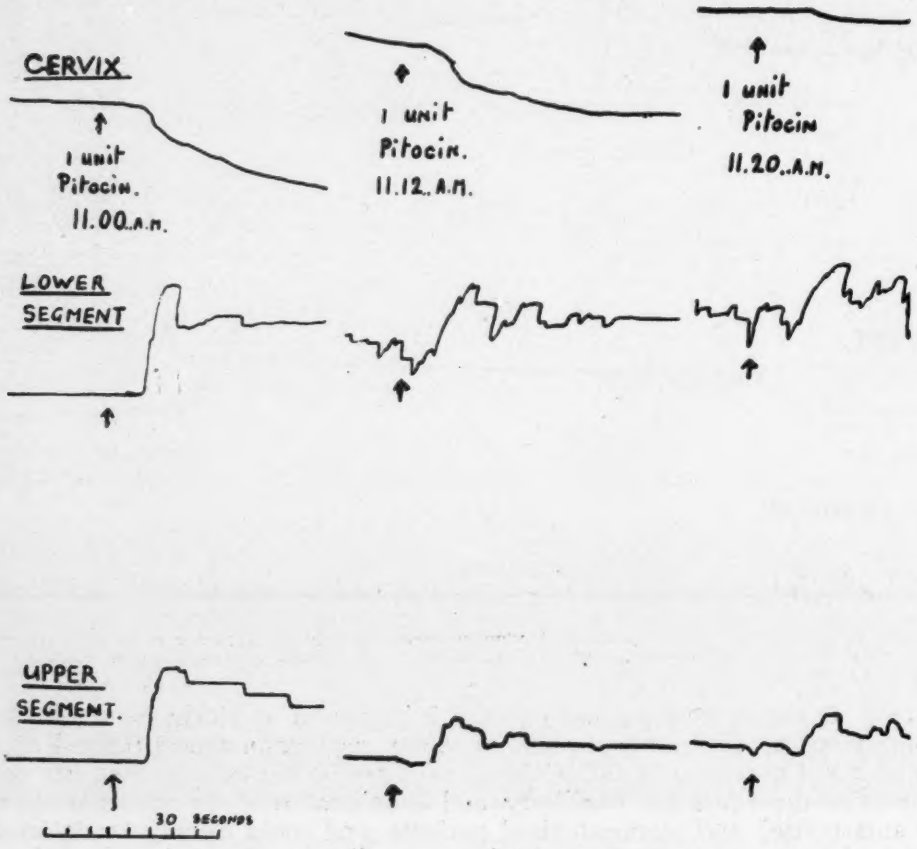

Fig. 8.—Triple cannula. Three times in succession intravenous oxytocin (Pitocin 1 u.) causes rise in intrauterine pressure and fall of intracervical pressure.

The clinical application of these findings can be seen, for example, in the treatment of abortion. Where a vis a tergo is required then oxytocin, which stimulates mainly the corpus, would be the drug of choice and *not* ergometrine since this might contract the cervix. At least 4 units of oxytocin are probably needed to produce an appreciable rise of intrauterine pressure in the first 10 weeks and 1 to 2 units from the twelfth to twenty-fourth week of pregnancy. Oxytocin can be given in repeated doses. Vasopressin is an active oxytocic but it does cause undesirable side effects (nausea, vomiting, rise of blood pressure). Whether the selective action of ergometrine on the lower part of the uterus in early pregnancy is maintained in labor is conjectural. If this were proved, then retention of the placenta after ergometrine injections is explicable.

Pharmacological Response and Histological Pattern of the Cervix Uteri

The observations of Danforth[14] have raised doubts in the minds of clinicians as to whether the cervix possesses muscular contractility. From his histological study it would appear that the cervix consists mainly of fibrous tissue. If this view is accepted then it would be difficult to reconcile it with the records just presented which indicate that the cervix of the pregnant human uterus has independent contractility.

Dr. P. E. Hughesdon[15] of the Department of Morbid Anatomy at University College Hospital Medical School has been studying by special staining technique the cervix at different epochs of life. Some of this material was provided from cases in which balloon recordings had been made. He has arrived at certain conclusions which may elucidate still further the findings of Danforth.

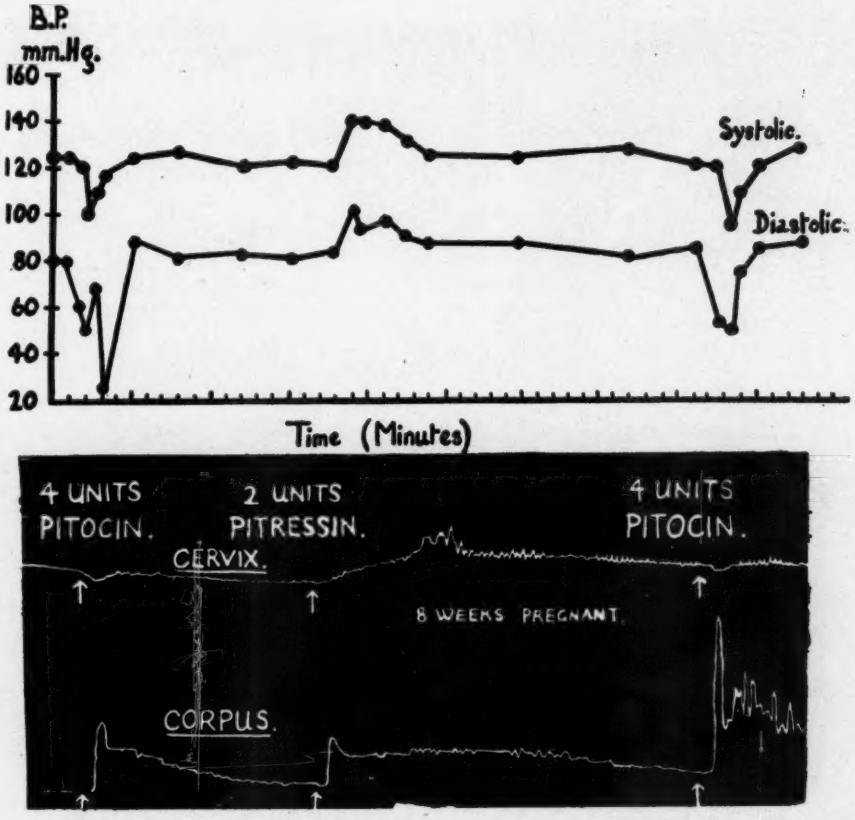

Fig. 9.—At 8 weeks: oxytocin (Pitocin) causes contractions of corpus, with slight fall of cervix pressure. Vasopressin (Pitressin) causes contraction of corpus, with slight rise of cervix pressure. Blood pressure falls with intravenous oxytocin, and rises with intravenous vasopressin.

General.—There is a continuous layer of smooth muscle running externally down the whole length of the uterovaginal canal, from the fundus to the vulva. This ground plan appears early and persists through life. The pattern matures during the last trimester of fetal life and at birth is similar to that of the adult (Figs. 10 and 11).

Fig. 10 is from a specimen obtained from an infant who died in the neonatal period (265 days maturity). It shows (1) posterior wall of bladder and uterovaginal canal, (2) continuous layer of muscle, fundus to lower vagina,

(3) further development of muscle in corpus in contrast to cervix, (4) leash fanning into portio. Fig. 11 is the same and shows point 4 under higher magnification.

In the corpus this external layer is looser than the rest and separated by wider collagen bundles. In the cervix it occupies in sections one-fourth to one-half of the thickness of the wall outside the mucosa; it will be referred to as the "extrinsic" muscle of the cervix. Below it is continuous with the vaginal muscle. The muscle fibers of this muscle are plump and stain well. They look mature and capable of function, they run in all directions and are not purely longitudinal. It must not be inferred that one-fourth to one-half the cervix is made up of muscle as such, for the "extrinsic" muscle is loose, with broad collagen septa (Fig. 12), as in the outer corpus.

Fig. 10.

Fig. 11.

Fig. 10.—Distribution of muscle (dark staining) in uterovaginal canal.
Fig. 11.—Muscle leash (←4) running into portio vaginalis of cervix.

Fig. 12 is taken from a cervix of a nullipara, aged 30 years, removed by Wertheim hysterectomy. It reveals (1) adenocarcinoma at upper end of cervical canal, (2) continuous layer of loose but well-formed muscle running from upper vagina up outer side of cervix, (3) leash fanning round fornix into portio.

The inner one-half to three-fourths of the cervix consists mainly of collagen, which gives it its normally tough consistency. The inner layers of the corporeal muscle above give place to collagen slowly at the isthmus.

In contradistinction Fig. 13 (from a para iii, aged 33 years, total hysterectomy, cervix, and lower corpus, posterior) shows (1) mucosal isthmus, indicated by group of dilated rounded acini, (2) solid mass of corporeal muscle above, (3) downward division of muscle into two main streams, an inner of immature and an outer of mature muscle, (4) the latter drawn up and everted by postvital retraction two-thirds of the way up the cervix, concealing its true importance. In an anterior specimen this layer is still further injured by dissection.

Fig. 12. Fig. 13.

Fig. 12.—Distribution of muscle in adult cervix (Wertheim hysterectomy).

Fig. 13.—Postvital retraction of muscles (X) (total hysterectomy), submucosal inner stream of immature muscle (Y).

Throughout this collagenous mass is dispersed a considerable quantity of mainly immature smooth muscle which will be referred to as the "intrinsic" muscle of the cervix. It runs in two main streams; (1) an outer stream which splits off from the extrinsic muscle when the fornices form and is carried down into the portio vaginalis (Figs. 10, 11, 12), and (2) an inner stream which hugs the mucosa (Fig. 13).

The intrinsic muscle fibers also run in every direction and are not purely circular. They are small, slender, and poorly staining, like the muscle of a small myoma. It is highly improbable that they have any functional effect. The contrasted appearance of the intrinsic and extrinsic muscle fibers (stained with Masson) are shown, respectively, in Figs. 14 and 15.

Fig. 14.

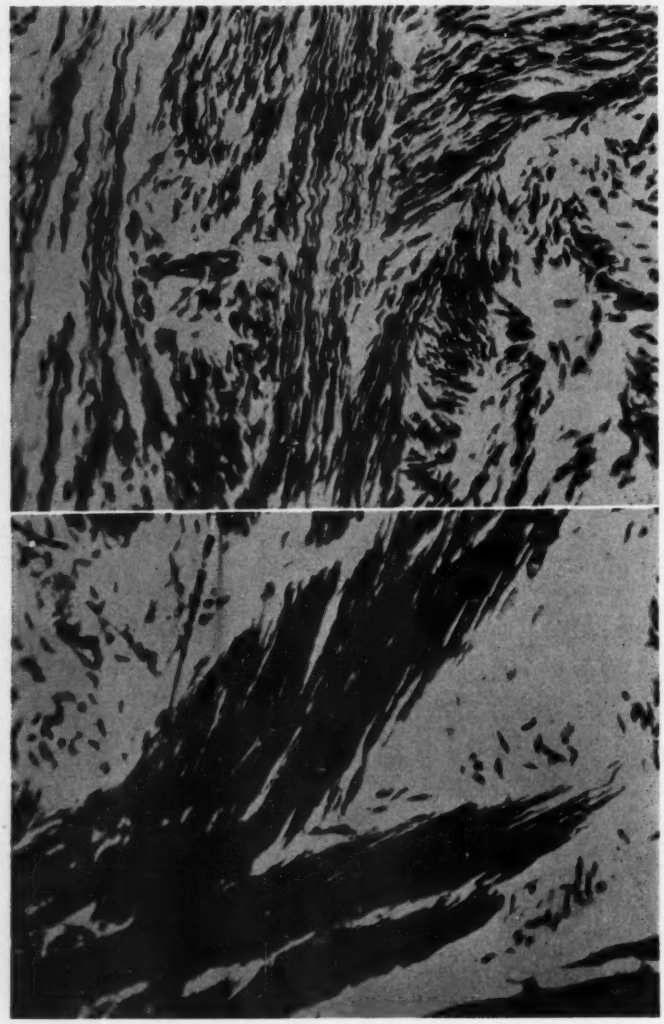

Fig. 15.

Fig. 14.—Intrinsic muscle fibers (immature). (×280.)
Fig. 15.—Extrinsic muscle fibers (mature). (×280.)

Figs. 14 and 15 (×280, Masson stain, green filter) are of a portion of the cervix of a woman 65 days pregnant. Immature (Fig. 14) and mature (Fig. 15) muscle fibers can be seen in the inner and outer zones, respectively.

There is a layer of fine elastic fibers just under the vaginal epithelium. At the fornix it turns down, like the inner part of the vaginal muscle, and runs for a variable distance toward the external os. It is present at birth. There is very little extravascular elastic tissue in the cervix.

The extrinsic muscle probably cannot independently influence the diameter of the nonpregnant cervix owing to the rigidity of its collagenous inner part. When the latter softens during pregnancy, however, there is no reason why it should not do so.

Artefacts of Cervical Structure Produced by Operation

Although the muscular ground plan of the cervix is clear and obvious in autopsy as seen in Fig. 16 (lower two-thirds of cervix of a primipara who died from postpartum hemorrhage showing [1] continuous layer of muscle exter-

Fig. 16.—Distribution of muscle in cervix in labor (death from postpartum hemorrhage).

nally, running up from vagina, [2] muscle occupying about half the thickness of the cervix, [3] internally the tissue congested and ecchymotic), and Wertheim material (Fig. 12), this is not so in uteri removed by vaginal or abdominal total hysterectomy, for the extrinsic muscle tends to be drawn up and everted by retraction. In an excised uterus the outer muscle layer is able to retract much more than the rest and this difference is so increased by fixation that in a uterus opened by a single longitudinal incision, especially if inadequate above, the cervix may be drawn up and point at right angles to its normal direction. In addition, dissection by the operator may fray the extrinsic muscle layer and make it ragged and unimpressive.

In Fig. 13, the retraction and eversion of the extrinsic muscle have taken it two-thirds of the way up the cervix. It is probable that Danforth[14] who used only hysterectomy material overlooked the importance of the extrinsic cervical muscle for these reasons.

Danforth[14] described the cervix as essentially collagenous. This is true of its bulkier inner part and he deserves credit for underlining it. For reasons explained above he overlooked the muscular character of its outer part, and his over-all account is therefore misleading. For example, it suggests the entirely false inferences that the cervix cannot contract and relax, and that its behavior can never be influenced by drugs. Possibly this is so but the reason is not anatomical.

It is in any case improbable that the main part of the cervix offers any serious resistance in labor; the muscular part is too slender and the collagenous part too softened by pregnancy. It is probable that the effective sphincter uteri is the far bulkier muscle mass of the isthmic region (Fig. 13), which forms the lower part of the lower segment and Fitzgerald[16] has provided clinical evidence in support of this.

Abnormal Uterine Action

The type of abnormal uterine action that I wish to consider is that where function is at fault and there is not any obvious mechanical obstruction to delivery. When cephalopelvic disproportion is present there is the usual sequence of premature rupture of the membranes, weak contractions, and a cervix that dilates slowly.

TABLE I. COMPARATIVE DATA OF UTERINE INERTIA

AUTHORS	NUMBER OF CASES	INCIDENCE OF INERTIA (PER CENT)	MINIMUM DURATION OF LABOR (HOURS)	MATERNAL MORTALITY PER 1,000 BIRTHS		COMBINED FETAL MORTALITY PER 1,000 BIRTHS	
				TOTAL CLINIC FIGURES	INERTIA	TOTAL CLINIC FIGURES	INERTIA
Odell et al. (1945)	15,824	2.7	30	—	7	—	104
Schmitz et al. (1947)	5,599	4.0	24	—	0.0	26	38
Douglas and Stander (1943)	25,574	9.0	30	1.59	2.79	37.7	87.6
MacRae (1949)	19,745	3.2	48	1.52	4.75	46.53	120

Of late years there has been a shift of emphasis from pelvic structure to that of uterine function. Attempts have been made to classify inefficient uterine action and Jeffcoate's[17] classification does reconcile most of the clinical and experimental observations so far recorded.

The definition of what constitutes a prolonged labor varies from clinic to clinic. Uterine inertia is a term used to cover a variety of abnormalities of uterine function. Jeffcoate restricts the use of the term to the uterus that is inactive or only feebly active in all areas. Eastman[18] has defined uterine inertia as follows: "In the first stage sluggishness of uterine contractions (after true labor has begun) of such a degree that (1) the cervix shows no change over an 8-hour period and (2) the uterine wall is easily indentable at the acme of each pain; in the second stage sluggishness of uterine contractions of such a

degree that the head neither rotates nor descends over a 2-hour period with a uterine wall which is easily indentable at the acme of each pain."

MacRae[19] has analyzed the 10-year period, 1939-1948, and found that 3.2 per cent of deliveries at Queen Charlotte's Maternity Hospital, London, lasted 48 hours or more.

Table I has been reproduced from his paper and gives comparative data as to incidence and mortality.

The Hazards of Long Labor

From time immemorial the danger of long labor has been appreciated by all who tended women in childbirth. Hugh Chamberlen (1683) who translated the second edition of Mauriceau's book, *The Diseases of Women With Child and in Childbed* described "going with child is as a rough sea, on which a big-bellyed woman and her infant floats the space of nine months. And Labour which is the only Port, is so full of dangerous Rocks."

Dr. H. L. Hartley of the Department of Statistics, University College, London, with the assistance of Dr. Wendy Greengross of the Obstetric Unit, has analyzed samples of deliveries over the years 1946 to 1949. The labors were grouped according to duration in hours—under 24, 24-36, 36-48 and over 48. The four duration classes were used as strata and a larger sampling fraction was used for the long duration classes. Graphs have been prepared of the factors which are statistically significant (Figs. 17, 18, 19, and 20).

These serve to show the danger of long labor to both mother and baby.

Prolonged labor is the greatest single cause of *shock*. Sheehan[20] has found that the risk of death from shock increases in those cases of vaginal delivery after a labor lasting 2 to 4 days or more. In his series of autopsies there was not one death from shock in patients delivered within 24 to 48 hours no matter how brutal the delivery.

Intrauterine Infection.—It has long been held that the incidence and severity of intrauterine infection was directly related to the length of the labor and the time the membranes had been ruptured. In my experience the number of vaginal (or rectal) examinations is an important factor, and intraperitoneal and uterine cultures at the time of cesarean section support this impression.

Fetal Risks.—Intrapartum infection of the fetus is a real danger as reported by Douglas and Stander[21] who discovered 83 cases of bacteremia in stillborn infants after long labor. Anaerobic streptococcus was the most frequent organism. MacRae,[19] at Queen Charlotte's Maternity Hospital, London, has also found a high fetal loss due to intrauterine infection. He suggests that a sample of cord blood should be taken for culture in cases where the membranes have been ruptured for a long time. The prophylactic use of sulfonamides and antibiotics might help to reduce this risk.

Treatment of Long Labor

Prophylactic Treatment.—Is it possible to prevent long labor? This complication is more prevalent among primiparas, irrespective of age. As so often an obvious and tangible cause cannot be found, it is not unreasonable to assume that a psychogenic element might play a part in etiology. The pain-fear-tension syndrome of Dr. Grantley Dick Read is known to all. Many of the older writers were aware of this and Samuel Merriman, a lecturer in midwifery at The Middlesex Hospital, London, writing in 1820, has reminded us that "Practitioners of all ages have agreed that the action of the uterus is very much influenced by the mental powers. Evidence of this is to be found in many medical

records: and the fact is presented to our view in many occurrences of common life. It is, therefore, to be considered of importance that the mind of the parturient woman should be kept as easy and tranquil as possible." DeLee believed in this also, and it was his support which was the greatest encouragement to G. D. Read to continue his work. I would add that more important than

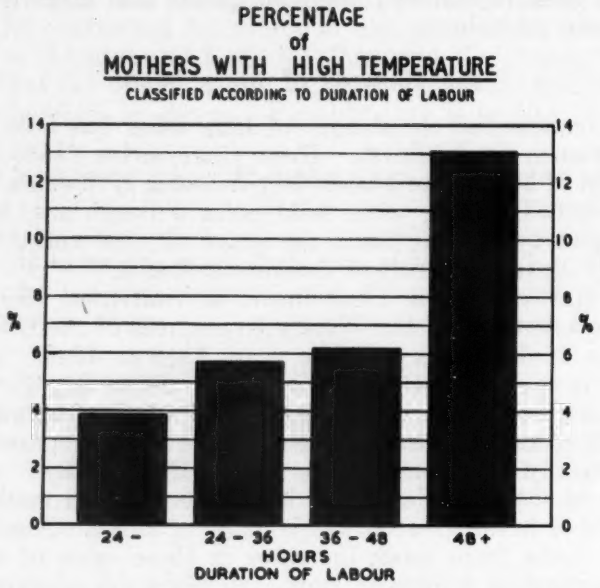

Fig. 17—Percentage of mothers with notifiable pyrexia classified according to duration of labor.

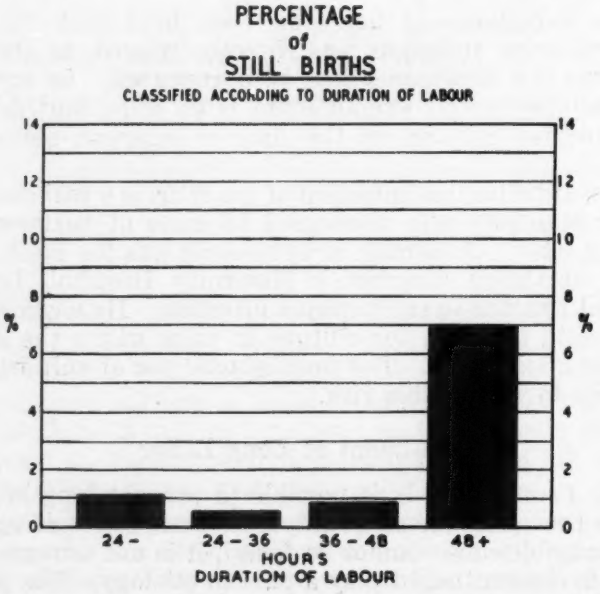

Fig. 18.—Percentage of stillbirths classified according to duration of labor.

any training during the antenatal period is the attitude of the attendants to a woman in labor. The way in which they support a parturient woman will sometimes decide the kind of labor she is going to have. Fluid balance, adequate

nutrition, active movement early in the first stage, a timely sedative, the prevention of acetonuria by intravenous glucose—all will contribute toward the prevention of protracted labor.

Treatment of Established Uterine Inertia.—When should a labor be considered prolonged? In most British clinics a labor comes into this category

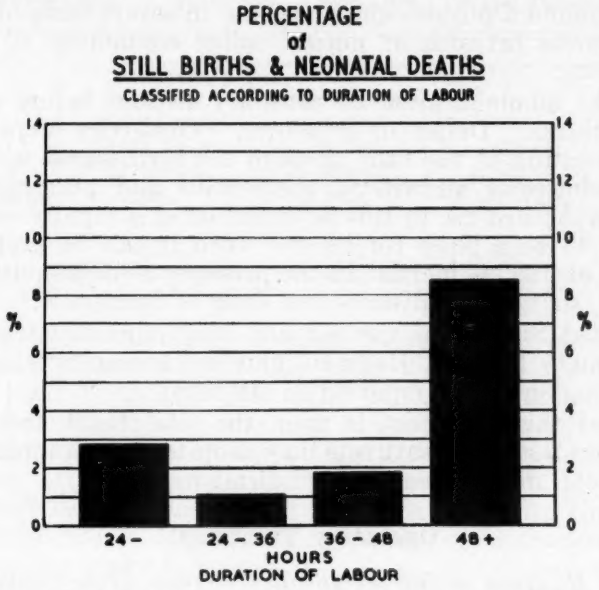

Fig. 19.—Percentage of stillbirths and neonatal deaths classified according to duration of labor.

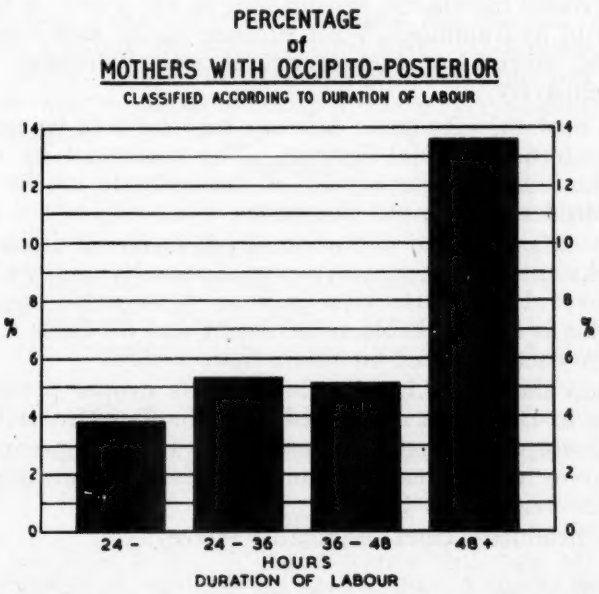

Fig. 20.—Percentage of mothers with occipitoposterior positions classfied according to duration of labor.

when it has lasted 48 hours. I believe this ceiling is too high and that it should be dropped to 24 hours. A vaginal examination is always necessary at this time and the labor should be carefully reviewed.

Medical Treatment.—Further sedation may be necessary and after a period of mental rest the woman may deliver herself normally. The treatment of this condition lends itself to much abracadabra and many baseless claims have been made for different drugs.

Intravenous Oxytocin Infusion.—One of the first to describe this method was Page[22] who found a physiological response in severe cases of uterine inertia after an intravenous infusion of normal saline containing 10 to 20 units of Pitocin to the liter.

To many the administration of pituitary extract before delivery of the placenta is anathema. DeLee in a lecture, "Obstetrics Versus Midwifery," denounced the blasting of the baby through the birth canal with a solution of pituitary as meddlesome midwifery, unscientific and pernicious. All would agree that the haphazard use of this powerful drug is rightly condemned. But there does seem to be a place for its use when it can be properly controlled in selected cases of uterine inertia; in the presence of disproportion, malpresentation, excessive parity, fetal distress, the drug is dangerous.

In the United States this method has been clinically tested and proved (Reid,[23] Eastman,[24] Stone,[25] Hellman and collaborators[26]). Theobald and associates[27] in England have reported in its favor.

One effect of this treatment is upon the fetal heart and this cannot be ignored. At times the fetal heart rate may drop to an alarmingly low level and for this reason fetal distress is a contraindication.

Operative Treatment

1. Artificial Rupture of the Membranes.—Often after rupture of the membranes uterine action, previously sluggish, becomes active and the cervix rapidly dilates. In hypertonic inertia the resting tone of the uterus is abnormally high. This is also seen in hydramnios. With rupture of the membranes uterine tone is diminished and uterine contractions are thereby increased. The tocograph reveals this conclusively.

2. Cesarean Section.—At times delivery may have to be completed rapidly on account of maternal or fetal distress. The treatment by cesarean section of prolonged labor due to some variety of incoordinate uterine action is more frequently practiced now than in the past.

The over-all safety of the operation, irrespective of indication, has been revealed by Dieckmann.[28a] There was a period recently at the Chicago Lying-in Hospital when over 1,100 consecutive sections were performed without a maternal death. This is a remarkable achievement and all those concerned at that hospital should be congratulated on this unique record.

Marshall[29] has also put this operation into its proper perspective so far as obstetric practice in Britain is concerned. At the Twelfth British Congress of Obstetrics and Gynaecology held in London in 1949 he presented the results of a national survey of cesarean section operations performed at 16 teaching schools during the years 1943 to 1947.

Table II is produced from Marshall's survey.

TABLE II. RESULTS OF NATIONAL SURVEY OF CESAREAN SECTION OPERATIONS PERFORMED AT 16 TEACHING SCHOOLS, 1943-1947

TOTAL CESAREAN SECTIONS (ALL INDICATIONS)	MATERNAL DEATHS	MATERNAL MORTALITY
7,762	77	0.99%

Dieckmann[28b] has stated that the maximum total mortality rate for cesarean section should be 0.5 to 1.0 per cent, but, in the treatment of contracted pelvis, elective cesarean section should have a maximum maternal mortality of 0.2 per cent and after a test of labor of 0.4 per cent.

TABLE III. COMPARISONS OF MORTALITY (CONTRACTED PELVIS, DISPROPORTIONS, ETC.)

	A	B	C	D
	ELECTIVE CESAREAN SECTION AND LABOR UP TO 6 HOURS	AFTER A TEST OF LABOR UP TO 24 HOURS	OVER-ALL MORTALITY	OVER 24 HOURS IN LABOR EXCLUDING ONLY RUPTURED UTERI
Dieckmann's standards (1945)	0.2%	0.4%	0.5%–1.0%	—
Marshall (lower segment only)	0.12% (2,578 sections)	0.35% (848 sections)	0.99% (7,762 sections)	1.55% (1,160 sections)

With Dieckmann's standard in mind, Marshall has compiled Table III. Despite Marshall's observation on this table that "the woman delivered by transperitoneal lower segment section after 24 hours in labour incurs a lethal risk thirteen times greater than she does if operated on before the beginning of labour or within six hours of onset," I still hold that there is a real place for the treatment of prolonged labor by cesarean section. I am not alone in this for Lawrence[30] has reported that at the Leeds Maternity Hospital prolonged labor due to uterine inertia was, with the exception of contracted pelvis, the commonest indication for cesarean section.

Much harm has resulted from the teaching that delivery must be at all costs per vaginam because the membranes have ruptured. Unnecessary vaginal mutilation predisposing as it does to genital infection has resulted from the adoption of this inflexible attitude in obstetric practice. Abdominal delivery, when the os is only partly dilated, is accompanied with far less trauma than a vaginal associated with multiple incisions of the cervix, vaginal lacerations, and an extensive episiotomy.

Summary

1. The cervix uteri in early pregnancy has a contractility independent of the corpus and can respond to drugs.

2. Special histological technique has revealed an "extrinsic" and "intrinsic" musculature in the cervix uteri.

3. Some of the dangers of prolonged labor are shock, uterine infection, and fetal death.

4. Oxytocic drip infusion is valuable in the treatment of uterine inertia.

5. A plea is made for an extension of cesarean section in the treatment of prolonged labor.

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CLINICAL EVALUATION OF THE SILVER CARBONATE VAGINAL SMEAR METHOD IN THE DIAGNOSIS OF UTERINE CANCER*

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SINCE the introduction of the vaginal smear method for the diagnosis of uterine cancer by Papanicolaou and Traut,[1] numerous published reports indicate the usefulness of this procedure. A comprehensive survey of the world literature is included in the excellently illustrated monograph of Gates and Warren[2] and the most instructive book by the staff of the Vincent Memorial Hospital.[3]

With few exceptions those attempting to evaluate the so-called "cytological method" of cancer diagnosis have employed the Papanicolaou technique with meticulous care, especially with respect to details of fixation, choice of stains, and interpretation of the cytological characteristics of the smear. Without question this standardization of technique has greatly facilitated the teaching of a new diagnostic method and has made possible the rapid accumulation of a great wealth of material for its evaluation as a practical and accurate procedure.

In 1948 one of the authors (G. M. R.) together with associates[4] reported that exfoliated cells, as found in the vaginal smear, were readily impregnated with silver carbonate solution prepared according to the method of Del Rio Hortega.[5] Of particular importance was the observation that the chromatin material was remarkably argyrophilic. It was emphasized at that time that in view of the fact that the primary criteria for malignancy were nuclear characteristics, a distinctive nuclear stain would be most desirable. Since that time various of the technical aspects of the method have been thoroughly investigated and the method has been given a rigorous clinical trial. Our clinical experiences with the method during a three-year period are reported in this communication.

Method and Clinical Material

The complete details of the silver carbonate staining method as currently used in this laboratory together with the nuclear and cytoplasmic staining qualities of cells found in vaginal and cervical smears are reported in a separate communication.[6] The following summary of the method will be pertinent to the present report:

*This study has been supported by a grant from the Faculty Research Fund, University of Michigan.

Preparation of Smears.—During the first two study years (1947-1949) samplings of vaginal fluid and cervical secretions were obtained by aspirations with a glass pipette according to the method described by Papanicolaou.[1] During the third year a saline-moistened cotton applicator was used to obtain these smears. With very few exceptions a sampling of cells was obtained from (1) the posterior fornix of the vagina and (2) the cervical os at the squamocolumnar junction. The smear is made by rolling the applicator over the surface of the microscopic slide.

Fixation.—During the first two years of this study little care was taken to insure immediate fixation. In fact, the belief that more cells would be retained on a relatively dry smear resulted in the deliberate drying of many smears before fixation. During the entire third year of study the smears were immersed in 20 per cent formalin (1 volume formaldehyde diluted with 4 volumes distilled water) while still moist. It was felt that the quality of the stain was thereby improved. After fixation for at least 15 minutes, the smears may be allowed to dry or carried directly to the next solution.

Staining Procedure.—The staining procedure has remained virtually unchanged throughout the investigation. The fixed smears are rinsed in ammonia water (5 to 6 drops ammonium hydroxide per 100 c.c. of distilled water) and rinsed successively in 2 jars of distilled water. Individual slides are then placed horizontally on a staining rack and their surfaces covered with medium strength silver carbonate solution* for 2 to 3 minutes. The silver solution is then reduced by immersing the smear in 1 per cent formalin for 1 minute. While not an essential part of the procedure, a clearer background and one with few extraneous particles of reduced silver will be obtained if the formalin solutions for fixation and reduction are buffered to a pH of approximately 7. Following reduction, the smear is rinsed in distilled water, dried in air or rinsed successively in 90 per cent alcohol, absolute alcohol, xylol, and finally mounted in Clarite or balsam. It is of practical interest that the smears from approximately 1,500 subjects (three-fourths of the total number of subjects) were evaluated without the benefit of mounting. Although the unmounted smear lacks some of the advantageous physical properties of the conventional microscopic preparation, the several examiners who participated in this study were not convinced that the slight improvement in smear quality justified the several additional technical steps. It must be emphasized that the dried, silver-impregnated smear is entirely different from the conventionally stained smear in that the physical properties acquired by silver treatment with subsequent reduction render the cells quite satisfactory for microscopic study. There were notable instances when the additional technical advantages of clearing and mounting were utilized, e.g., any suspicious smear requiring more than routine study and any smear used in photomicrography.

Criteria for Malignancy.—In general, silver impregnation permits the utilization of the various criteria for malignancy that have been described by Papanicolaou[1] and others who have utilized the polychrome staining procedure. Although various authors have indicated that the presence of red cells or evidence of such cells may be a helpful adjunctive criterion of malignancy, we have not utilized this since bleeding was a very common complaint in this series. In the report of the results of the cytological diagnosis a description of the principal characteristics of the smear was given, together

*This dilution of silver carbonate is prepared by adding 1 volume of stock Hortega solution to 1 volume distilled water. The stock solution is prepared as follows: To 100 c.c. of 10 per cent silver nitrate add 300 c.c. of 5 per cent sodium carbonate. Carefully add ammonium hydroxide drop by drop (approximately 10 c.c.) with constant shaking until the precipitate is just dissolved. Avoid excess ammonium hydroxide, store solution in a brown bottle.

with a grading of the preparation. Grading was based upon the useful classification suggested by Papanicolaou, i.e., Class I, normal; Class II, atypical but not carcinomatous; Class III, suspicious for malignancy; Class IV, malignancy determined after studying several fields; and Class V, obvious carcinoma as indicated by many abnormal cells and extreme deviation from the normal. Examples of several of these classes are illustrated in the photomicrographs (Figs. 1-6).

Fig. 1.

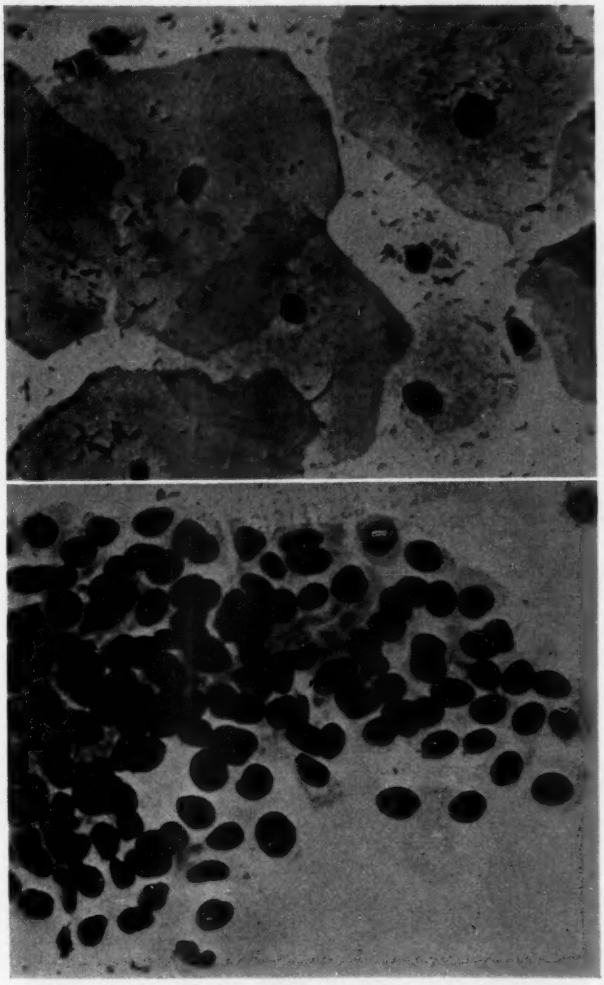

Fig. 2.

Fig. 1.—Normal superficial squamous cells, Class I. (×530.)

Fig. 2.—Normal basal cells in an atrophic smear from a postmenopausal subject, Class II. (×530.)

Not infrequently the routine procedure results in a very heavy silver impregnation of the nucleus. As a result, the nucleus may present a solid, amorphous appearance for which the technique may be criticized. The authors have not felt that this characteristic of the stain was a handicap, in fact, the intensity of the stain has served the useful purpose of attracting the examiner's eye to the suspicious cell. For the pathologist or trained cytological diagnostician who prefers the opportunity of studying chromatin detail it

must be emphasized that the silver impregnation is most adaptable and a little experience in changing the dilution of the Hortega solution or in modifying the staining time will result in virtually any degree of staining intensity desired.

In the event that a slide has stained too darkly by the routine method, it has been found very helpful to immerse it briefly in a 5 per cent solution of sodium thiosulfate. With a little experience, this will result in a demonstration of fine chromatin detail. It has been found especially useful where a diagnosis rests upon the condition of the nucleolus.

Fig. 3.

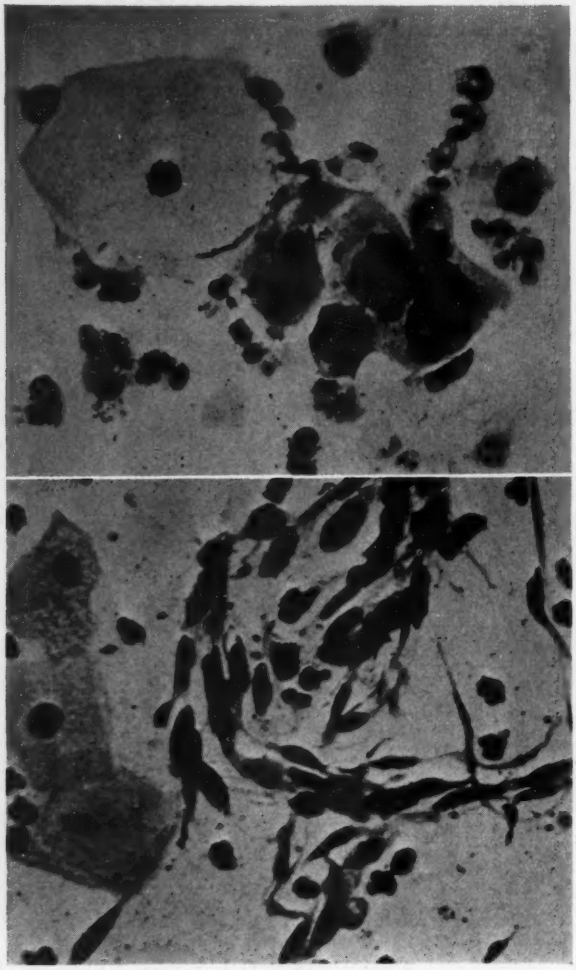

Fig. 4.

Fig. 3.—A small cluster of malignant cells adjacent to a normal noncornified superficial cell, cytological Class V. Poorly differentiated squamous-cell carcinoma of the cervix. (×530.)

Fig. 4.—Fiber-like cells in a case of highly differentiated squamous-cell carcinoma of the cervix, cytological Class V. (×530.)

Clinical Material.—Smears were obtained from patients on the gynecology service of the Department of Obstetrics and Gynecology at the University Hospital. The great majority of the subjects were outpatients who had various types of gynecological complaints justifying their examination and study in this department. Smears were obtained at the discretion of the gynecologist

whenever the history, symptoms, or clinical findings were such as to suggest the possible existence of carcinoma. The most common symptom was abnormal bleeding, either irregular or seemingly of a nonfunctional nature. The ages ranged from 13 years to 84 years, with an average age of 47 years. Seventy-eight per cent of the subjects were from 31 to 60 years of age. Over half (58 per cent) of the subjects were in the 41 to 60 age group. In the premenopausal subjects the most common clinical findings were hyper- and polymenorrhea, intermenstrual spotting, cervical erosion, or vaginal discharge. Patients who had a previous diagnosis of carcinoma of the uterus and who had been treated by irradiation or surgery or both are included and their smears have been classified in the routine manner. Smears were generally not obtained in cases of clinically obvious carcinoma.

Fig. 5.

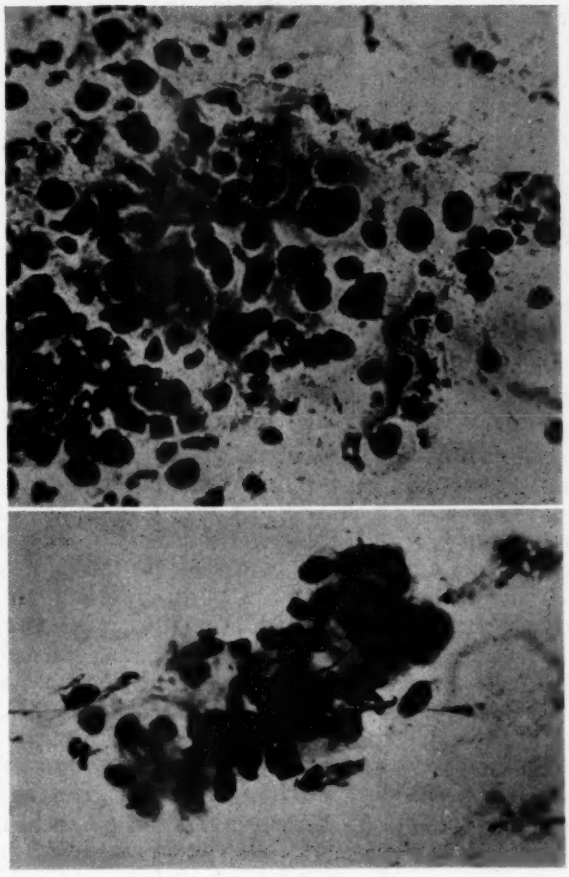

Fig. 6.

Fig. 5.—Atypical squamous cells showing a marked degree of nuclear variability. Smears graded Class IV although a diagnosis of carcinoma has not been confirmed. (×530.)

Fig. 6.—Cluster of atypical cells associated with adenocarcinoma of the endometrium, cytological Class IV. (×530.)

With few exceptions, the two smears for each patient were obtained at the time of the routine speculum examination. Following fixation, the smears were transferred to the cytological laboratory for evaluation. During the first two study periods (1947-1948 and 1948-1949) the information provided the examiner included the patient's age, and a brief statement of symptoms and clinical findings. During the third year (1949-1950) only the name and registration number were given the examiner.

TABLE I. DIAGNOSTIC RESULTS WITH SILVER CARBONATE STAINED VAGINAL SMEARS

PERIOD	EXAMINERS	TOTAL CASES	PROVED CANCER CASES IN SERIES	FALSE POSITIVE DIAGNOSES		FALSE NEGATIVE DIAGNOSES		TOTAL ERROR	
				NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
1947-48	Arcilla	484	21	2	0.40	8	1.65	10	2.1
1948-49	Behrman	670	50	7	1.05	7	1.05	14	2.1
1949-50	Riley, Dontas, De Vore	854	49	13	1.52	7	0.82	20	2.3
	Totals	2,008	120	22	1.09	22	1.09	44	2.2

Diagnostic Results

During the three-year period of this investigation slides satisfactory for evaluation were obtained from a total of 2,008 patients (Table I). During the first two study periods from September, 1947, to September, 1949, one examiner alone was responsible for staining and evaluating the smears. During the third period one author (E. D.) performed a preliminary screening in many instances before a final evaluation was reached.*

The total number of carcinoma cases in this series as proved by biopsies or endometrial curettements was 120. Of this number, 98 cases were correctly diagnosed, leaving a total of 22 undetected carcinomas. On the other hand, there were smears from a total of 1,888 gynecological patients wherein carcinoma was not detected clinically or pathologically and in only 22 instances were incorrect diagnoses of carcinoma reported. Thus, false positive reports were submitted in 1.16 per cent of these cases.

In brief, it appears that equally as many false negative reports were obtained as false positive ones. In all, there were a total of 44 incorrect reports with an over-all percentage error of 2.2 per cent. In a review of the cases where incorrect diagnoses of carcinoma were made there appears to be no consistent explanation for these errors. However, it was clear that the false positive diagnosis was most often reported in the presence of cervical erosion or cervicitis. In a few instances the pathological diagnosis of cervical erosion included comments on the presence of "atypical squamous epithelium." Without question these deviations from normal squamous-cell proliferation complicated the evaluation of some smears.

We were especially concerned that a fairly high percentage (18 per cent) of the proved carcinoma cases were not detected. These cases, together with the pathological diagnosis, are listed in Table II.

Fifteen, or 68 per cent, of the errors are attributable to failure to detect adenocarcinoma of the endometrium (10 cases) or cervical carcinoma in situ (5 cases). In one instance (Case No. 683121) a cervical biopsy by the referring physician had been diagnosed as cornifying squamous-cell carcinoma of the cervix. Although the microscopic slides in this case were reviewed by the pathologists in this hospital and the diagnosis confirmed, a second cervical biopsy at the time smears were obtained did not reveal carcinoma. In another instance (Case No. 656821) a biopsy of a vesicovaginal fistula resulted in a diagnosis of squamous-cell carcinoma. In this case the fistula appeared obviously carcinomatous upon first inspection yet a total of 7 smears did not permit a positive diagnosis of carcinoma. The remaining 5 cases where a positive diagnosis was not made included 4 cases of squamous-cell carcinoma of the cervix and 1 case of adenocarcinoma of the cervix. It should be pointed out that with three exceptions the smears in these false negative cases were all graded as containing atypical cells (10 cases) or suspicious cells (9 cases).

Discussion

The main objective of this investigation was not to evaluate the cytological method as a means of diagnosing uterine carcinoma. This has been most ably undertaken by numerous pathological or cytological specialists, often in laboratories especially created and staffed for the purpose, using common or similar technical procedures. The present study has provided an opportunity to test the accuracy and practicability of a new technical procedure under a special set of investigative conditions. These conditions include (1) the

*During this period valuable technical assistance was given by Barbara De Vore, Research Assistant.

TABLE II. PATHOLOGICAL DIAGNOSIS IN CASES WHERE CARCINOMA WAS NOT DETECTED BY THE VAGINAL SMEAR METHOD

NO.	REGISTRATION NO.	CLASSIFICATION OF SMEAR	PATHOLOGICAL DIAGNOSES	SOURCE OF TISSUE STUDIED
1.	638106	II	Well-differentiated adenocarcinoma of endometrium, slight squamous metaplasia	D. & C.
2.	308053	II	Well-differentiated papilliferous adenocarcinoma of the endometrium, Grade III	D. & C.
3.	627708	III	Papilliferous adenocarcinoma of the endometrium, Grade II	D. & C.
4.	636989	III	Adenocarcinoma of endometrium with metaplasia to squamous-cell type	D. & C.
5.	648274	III	Early adenocarcinoma of endometrium	D. & C.
6.	660056	II	Well-differentiated adenocarcinoma of endometrium.	D. & C.
7.	303355	III	Early adenocarcinoma of endometrium	D. & C.
8.	684094	I	Well-differentiated papilliferous adenocarcinoma of endometrium. Dilatation and curettage before referral to this department	D. & C.
9.	682290	II	Papilliferous adenocarcinoma of endometrium. Dilatation and curettage before referral to this department	D. & C.
10.	451733	I	Moderately well-differentiated adenocarcinoma of endometrium	D. & C.
11.	555747	III	Adenocarcinoma of cervix infiltrating all material submitted	Cervical biopsy
12.	631037	III	An area of disarranged epithelial cells, probable carcinoma in situ	Cervical biopsy
13.	633025	II	Small fragments of cervix show epithelial proliferation which is so atypical that it justifies a diagnosis of squamous-cell carcinoma. Squamous-cell carcinoma, largely intramucosal	Cervical biopsy
14.	633218	II	Detached fragment of medullary squamous-cell carcinoma	Cervical biopsy
15.	650808	II	Intraepithelial carcinoma	Cervical biopsy
16.	661552	III	Intraepithelial carcinoma	Cervical biopsy
17.	647745	III	Infiltrating carcinoma of cervix	Cervical biopsy
18.	684887	II	Poorly differentiated squamous cell carcinoma of cervix	Cervical biopsy
19.	671993	II	Noncornifying medullary squamous-cell carcinoma of cervix	Cervical biopsy
20.	645796	II	Cervical carcinoma, in situ	Cervical biopsy
21.	683121	I	Cervical biopsy at time of smear, negative for carcinoma. Previous biopsy by referring physician, cornifying squamous cell carcinoma of cervix	Cervical biopsy
22.	656821	III	Squamous-cell carcinoma	Biopsy of vesico-vaginal fistula wall

use of smears from gynecological patients exclusively, and (2) evaluation of smears by individuals who previously had had no special training or experience with the technical procedure or cytological methods.

In our hands, under relatively rigid trial conditions, the accuracy of the silver method compares very favorably with that reported by other investigators (Table III). The listed percentage errors should not be interpreted as reflecting a precise difference between polychrome and silver methods, since the several studies were carried out under variable conditions including differences with respect to number of cases, number of slides studied per case, and number of cases with symptoms. It is well appreciated that the percentage error will be low when a series is comprised mainly of normal subjects. This largely explains the difference in accuracy reported by Gates and Warren[2] for two different sampling populations. Reicher and associates[12] also note that any large series dilutes the percentage of error with benign cases. In their series approximately one out of every 41 patients studied was found to have a malignant lesion. In the series studied by means of the silver stain, one out of 17 patients had a pathological diagnosis of uterine malignancy.

TABLE III. COMPARATIVE DIAGNOSTIC ACCURACIES FOR PAPANICOLAOU AND SILVER STAINING METHODS

REPORTED BY	STAINING METHOD	TOTAL CASES	TOTAL PROVED CANCER CASES IN SERIES	TOTAL ERROR	
				NO. OF CASES	%
Jones, et al.[8] (1945)	Papanicolaou and modification	427	82	16	3.7
Meigs, et al.[9] (1945)	Papanicolaou	1,015	154	41	4.0
Scheffey and Hoffman[10] (1948)	Papanicolaou	500	63	26	5.2
Fremont-Smith, et al.[11] (1948)	Papanicolaou	5,621	492	136	2.8
Gates and Warren[2] (1950)	Papanicolaou				
Group I*		1,300	81	33	2.5
Group II†		292 (smears)	45	20 (smears)	9.0
Reicher, et al.[12] (1950)	Papanicolaou	3,500	85	26	0.7
Present study (1950)	Silver	2,008	120	44	2.2

*Reported as consisting of 1,300 smears from 1,300 patients taken as a routine procedure in cancer clinics.

†Based on 292 smears from 201 patients obtained in a gynecological outpatient clinic, cases which had been previously radiated excluded. Includes only cases diagnosed as definitely positive or negative.

The incentive to test the silver impregnation method arose from recognition of the fact that most of the reported criteria for malignancy depended upon characteristics of the nucleus. Although silver carbonate solution is excellent for the demonstration of such cytological details as reticular fibers and neural elements, the nuclear staining property of the solution is best demonstrated in a thin spread of exfoliated cells. It was but natural that a stain with such amazing affinity for the nucleus should be adapted to the cytological method of diagnosing uterine carcinoma.

The results described above leave something to be desired, especially with respect to accuracy. Although the over-all accuracy attained with the method compares most favorably with that reported by others using conventional stains, the authors feel that greater accuracy should be sought and probably

can be attained. It is probable that fewer errors would have been made had each of the several examiners had special training in the many details of the normal and pathological cytology of exfoliated cells. The importance of experience is indicated by the fact that one author (J. S. B.) had a 3 per cent error on his first 200 cases, 2 per cent on the second, and slightly less than 1 per cent on the third 200 cases. On the other hand, from a practical standpoint, it is indeed encouraging that relatively little experience was needed with this new technique to produce very gratifying results.

Superficially, the greatest defect in the procedure appears to be with respect to detection of endometrial carcinoma. As indicated earlier, almost half of the false negative reports were due to failure to diagnose this type of malignancy. Among the explanations that may be offered are: (1) failure of the examiner to recognize the malignant cells; (2) inadequate staining of the endometrial cells; and (3) failure to obtain samplings of the malignant cells. It is probable that all these circumstances contributed to the relative inaccuracy in detecting endometrial carcinoma. However, a re-examination of the smears suggests that the greatest single cause of error was the absence of diagnostically significant atypical endometrial cells in the smears submitted for study.

In several cases it is possible that operative manipulations attendant upon diagnostic dilatation and curettage previous to referral to this department may have reduced the chances of recovering endometrial cells. In a few instances suspicious cells were overlooked. One may wonder whether or not awareness of the clinical symptoms by the smear examiner would have encouraged him to look more exhaustively for the malignant cells. In a sense the plight of the examiner may be compared to a foxhound about to embark upon the hunt without the scent of the fox.

For the most part these same explanations could be applied to the failure to diagnose five cases of intraepithelial carcinoma and the six cases of invasive carcinoma. Pertinent is the fact that none of the examiners were impressed that poor staining contributed significantly to the incorrect diagnoses.

The twenty-two cases incorrectly diagnosed as carcinoma reflect the occasional inability of these examiners to distinguish between a high degree of aberration within normal limits and true malignancy. This is most strikingly illustrated in Fig. 5. This smear was graded Class IV although cervical biopsies on two occasions, repeated cervical examinations, and later smears did not support a diagnosis of carcinoma.

It will be recalled that a smear is obtained from both the posterior vaginal fornix and the squamocolumnar junction of the cervix. The latter smear affords the best opportunity to detect cervical carcinoma. Without question some method of sampling the endometrial cells is necessary other than the endocervical and vaginal aspirating or swabbing methods as employed in this study. Perhaps, as suggested by Papanicolaou and Marchetti,[7] direct aspiration of the uterine cavity would ensure greater success in recovering endometrial cells.

From a technical standpoint, several features of the silver carbonate method may be emphasized. Immersion of the fresh smear in formalin fixative results in loss of erythrocytes through hemolysis. This often serves the useful purpose of changing what originally may have been little more than a heavy deposit of red cells with a few partially obscured epithelial elements to an entirely satisfactory spread of epithelial cells.

There is a great difference in the physical properties of the smear impregnated with silver as compared with a polychrome stained smear. The latter technique utilizes fixatives and stains that provide a high degree of transparency of the cells and accompanying secretions. While this makes it possible

to visualize elements that might otherwise be obscured, the brilliance of the preparation may be most disagreeable and fatiguing to the microscopist. Silver-impregnated smears are characterized by a soft opacity which nevertheless permits microscopic visualization to a desirable depth. This combination of qualities facilitates cytological study especially when many slides are to be examined or a single slide is to be very carefully scrutinized. In addition to this advantage, the pronounced argyrophilic properties of chromatin material as displayed in exfoliated cells so accents nuclear details that deviations from normal are quickly seen.

While evaluating the silver method the authors could hardly avoid facing the problem of whether or not the results obtained with the vaginal smear method justify the work involved. Would it not be better to rely on the clinical findings and biopsy reports than attempt to utilize a technique with some acknowledged degree of error? We must agree with those who believe that the vaginal smear method is a definite adjunct to other well-established diagnostic procedures. One of the present authors (J. S. B.) pointed the way through smear diagnosis to the detection of three previously unsuspected cases of carcinoma including two cases of intraepithelial carcinoma and one early cervical carcinoma. Such experiences have been reported by others utilizing the cytological method. To insure a permanent place in our diagnostic armamentarium the method must prove practical and accurate. It is felt that the silver staining method, through simplification of technique and utilization of argyrophilic properties of the nucleus, aids in the fulfillment of these requirements.

Summary

1. A summary of the technical details of the silver carbonate staining method for vaginal smears is presented and the qualities of the stain are illustrated by photomicrographs of normal, suspicious, and malignant cells.

2. During three successive years (1947-1950), three different examiners evaluated smears from a total of 2,008 gynecological patients whose history or clinical findings were suspicious for carcinoma of the uterus.

3. The total number of carcinoma cases in the series was 120. Of this number, 98 cases were correctly diagnosed, leaving a total of 22 (18 per cent) undetected carcinomas. In the series of 1,888 patients without pathologically diagnosed carcinoma, 22 false positive diagnoses (1.2 per cent) were submitted. The total percentage error based on the total number of cases studied was 2.2 per cent.

4. It is pointed out that the accuracy attained with this procedure compares favorably with that reported by others using conventional polychrome stains. Although additional experience with the cytological method and especially with the characteristics of silver-impregnated cells may be expected to result in fewer errors, improvements in methods for obtaining the cell samplings, especially from the endometrium, will tend to reduce the number of missed carcinomas.

5. The experiences of the investigators with the silver technique during this trial period suggest that it may have certain practical advantages over polychrome procedures. Among these advantages are simplicity, rapidity, ease of examination, and the facility with which nuclear aberrations are recognized. These qualities, together with the observed accuracy, should prove of value in the application of cytological methods for the detection of carcinoma.

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CYCLIC VARIATIONS IN THE ENDOCERVIX*

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CYCLIC variations in the human endometrium are well defined and the different phases are easily recognizable microscopically. Novak and Everett[1] described definite but less striking cyclic changes in the endosalpinx of the human uterine tube. Changes in the human vaginal mucosa also occur; but observers are not in complete agreement as to their details.

Cyclic changes in the endocervix have also been reported, particularly by Wollner.[2-5] He described changes which followed a cycle corresponding to the phases of the endometrial cycle. The peak of development occurred just prior to the onset of the menstrual period. His cervical findings for each phase of the menstrual cycle are as follows:

Early proliferative phase: The surface epithelium is low columnar, with deeply stained, oval, basal nuclei and well-defined cells in continuous layers. There are scant glands with narrow lumina devoid of secretion. The glandular epithelium is low columnar. The stroma is dense and fibrous with collapsed vessels.

Late proliferative phase: The high columnar surface epithelium contains deeply stained oval, basal nuclei. The sparse glands are widely separated. The epithelium of the glands is similar to the surface epithelium and the individual cells are well defined. The stroma is moderately cellular.

Early secretory phase: The glands are numerous and variable in size and shape, with numerous projections into the lumina. The lining epithelium is high, containing much cytoplasm. The nuclei are elongated and have migrated to the center of the cell. The stroma is edematous with prominent vessels.

Late secretory phase: The epithelium is high columnar with ill-defined bulging cells and indistinct basal nuclei. The stroma is cellular with thick-walled arterioles.

Menstrual phase: The glands are sparse and regular with collapsed lumina. The cell lining is columnar with pyknotic nuclei. The stroma is dense with pyknotic nuclei and thick-walled blood vessels.

Sjovall[6] has also described cyclic changes in the endocervix. His description differs from the foregoing in that the peak of the change is reached during the middle of the menstrual cycle. He emphasized the presence of papillary projections which reach a maximum of development during the early secretory phase. He was unable to confirm Wollner's observation of a widespread desquamation at the time of the menstrual period. Papanicolaou, Traut, and Marchetti[7] describe cyclic changes similar to those described by Sjovall.

Schroeder[8] could not find cyclic changes in the endocervix because of the individual variability of the cervical mucosa. Recently, Topkins[9] was unable to establish a cycle in the endocervix when he compared 150 cervical biopsies with 150 endometrial biopsies.

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*Presented before the Chicago Gynecological Society, Feb. 16, 1951.

TABLE I. SURFACE EPITHELIUM*

	PROBABILITY†	PROLIFERATIVE						SECRETORY						MENSTRUAL		
		EARLY			LATE			EARLY			LATE					
Number of Cases		11			10			14			12			8		
Observer		A‡	B‡	X§	A‡	B‡	X§	A‡	B‡	X§	A‡	B‡	X§	A‡	B‡	X§
Criteria																
High columnar epith.		100	100	100	80	100	80	72	86	86	58	75	84	75	100	75
Secretion on surface	<0.05	36	73	64	30	50	60	57	86	72	42	67	75	75	12	37
Nuclei, basal	<0.01	82	91	91	80	80	100	72	79	79	84	84	100	100	100	100
Oval	<0.05	82	82	64	90	90	80	86	79	79	92	84	92	75	100	75
Deeply stained	>0.05	73	64	55	40	70	70	93	86	79	84	92	75	63	75	63

*All results expressed in percentages of total cases examined.
†Probabilities less than 0.05 are significant, greater, nonsignificant.
‡Columns A and B are expressed in percentage of positive findings for each criterion by observers A and B.
§Percentage of agreement between observers on total identical slides studied.

TABLE II. DETAILED OBSERVATIONS, GLANDS*

	PROBABILITY†	PROLIFERATIVE						SECRETORY						MENSTRUAL		
		EARLY			LATE			EARLY			LATE					
Number of Cases		11			11			15			12			9		
Observer		A	B	X‡	A	B	X‡	A	B	X‡	A	B	X‡	A	B	X‡
Criteria																
Many glands	<0.01	73	64	91	82	82	100	74	87	74	67	84	84	78	56	78
Simple glands	<0.05	64	45	45	73	55	64	87	33	47	58	33	67	33	45	89
Narrow lumen	>0.05	82	45	55	91	64	55	53	33	53	50	42	92	78	56	56
Secretion in lumen	<0.05	55	82	73	45	64	45	93	100	93	92	100	92	56	22	45
High columnar epith.	----	100	100	100	100	100	100	100	100	100	92	100	92	78	100	78
Cells distinct	>0.05	100	82	82	64	55	73	93	60	67	92	42	50	78	78	78
Nuclei, basal	----	100	82	82	100	100	100	87	87	100	100	100	100	100	89	89
Oval	<0.01	82	91	91	91	91	100	74	67	80	84	92	75	67	89	56
Large	>0.05	82	55	55	64	64	45	53	87	67	33	67	67	56	78	33
Deeply stained	<0.05	64	55	55	55	82	36	74	100	74	84	100	84	56	100	56

*All results expressed in percentages of total identical slides studied.
†Probabilities less than 0.05 are significant, greater, nonsignificant.
‡Percentage of agreement between observers.

There have been many studies of the cervix in animals including the study of the cow by M. Cole,[10] the ewe by H. Cole,[11] and the guinea pig by Jurow,[12] Sjovall,[6] and Hartmann and Olbers,[13] to mention only a few. Although many of the studies suggest possible cyclic variation their direct application to the human being is not valid.

It has long been observed clinically that there is a cyclic variation in the amount and the character of the cervical mucus. Seguy and his co-workers,[14] Pommerenke and Viergiver,[15] and others described a change in the viscosity and amount of the cervical mucus at midcycle when the penetrative power of the spermatozoa is the greatest. This occurs at about the time of ovulation in the female as demonstrated by basal temperature curves.[16]

Atkinson, Shettles, and Engle[17] cytochemically studied the secretion of mucus by the endocervical glands. They found that the active secretion of mucus into the lumina of glands was rhythmic with the largest quantity secreted at midcycle with smaller quantities near the time of the menstrual period. In the cervices of postmenopausal women little mucus was secreted, while during pregnancy large amounts of mucus were present.

Sjoval also described the histology of the endocervix in fourteen cases of endometrial hyperplasia. He examined material from six autopsy or hysterectomy specimens and eight cases with biopsies from the endocervix and the endometrium in each case. Sjovall described "a uniform pattern in the cervix." There were numerous glands close together in ten cases. The epithelium varied in height but in general was high with long cylindrical nuclei close together near the basement membrane. However, the most characteristic finding was the presence of papillary excrescences of the glandular epithelium. In the papillary projections the nuclei were larger and more numerous. Sjovall concluded that papillary excrescences were directly proportional to the activity of the mucosa, which in turn was an active picture of estrogenic hormonal stimulation.

In summary, there are clinical indications of cyclic variations in the cervix. The literature, however, contains contrasting viewpoints as regards the presence and exact type of histological variation in the endocervix.

Material and Methods

Fifty-eight cervices were selected from total hysterectomy specimens where sections of endometria and adequate clinical histories were available. The cervical specimens were grouped according to the phase of the menstrual cycle into early and late proliferative, early and late secretory, and menstrual on the basis of the findings in the endometria and the histories. One author, initially, studied the cervices making a detailed tabulation of the criteria described by Wollner.[2, 3, 4] Subsequently the second studied the same material in a similar manner but without knowledge of the detailed findings of the first study. In addition, three other groups of cervices were studied. Fifteen were selected from postmenopausal patients, thirty from cases of endometrial hyperplasia,[18] and a group including fifteen normal and fifteen showing only chronic cervicitis were chosen for comparison.

Thus, a total of 133 cervices were examined in this study. The cervix was cut longitudinally to include the squamous epithelium and the entire length of the endocervix in nearly every case. No biopsies were included as they

TABLE III. DETAILED OBSERVATIONS, STROMA*

	PROB-ABILITY†	PROLIFERATIVE						SECRETORY						MENSTRUAL		
		EARLY			LATE			EARLY			LATE					
Number of Cases		11			11			15			12			9		
Observer		A	B	X‡	A	B	X‡	A	B	X‡	A	B	X‡	A	B	X‡
Criteria																
Dense stroma	>0.05	45	36	55	45	36	36	33	40	67	92	92	84	45	33	67
Edema	<0.01	55	64	55	64	64	82	74	67	67	8	8	84	56	67	89
Red blood cells	<0.05	27	0	73	18	0	82	20	13	67	16	0	84	22	0	78
Nuclei, large	>0.05	45	0	55	73	45	73	74	0	26	84	16	33	33	0	67
Deeply stained	>0.05	73	100	73	55	82	55	26	100	26	25	100	25	45	100	45
Vessels, few	>0.05	18	55	45	64	64	64	7	53	53	25	16	75	11	89	22
Collapsed	>0.05	27	64	64	64	55	73	20	60	60	25	33	42	11	78	33

*All results expressed in percentages of total identical slides studied.
†Probabilities less than 0.05 are significant, greater, nonsignificant.
‡Percentage of agreement between observers.

were not considered to reflect the complete histological pattern of the endocervix. Special stains for glycogen, mucus, and cilia were prepared in four cases, but the information obtained did not justify further employment of these stains.

Results

A. Cyclic Change.—Considerable difficulty has been experienced in the attempt to present the data in an easily understandable tabular form. Originally the data were presented as an average of the findings of the two observers. There were, however, in many groups rather marked variations between the findings of the two observers. It did not, therefore, seem valid to present the data in such a fashion. Consequently the findings of each observer in the study on cyclic changes are presented in the first three tables for the benefit of those readers who are interested in checking the detailed data.

Cyclic trends in the detailed criteria, as claimed by Wollner, are conspicuous mainly by their absence. In a few instances trends are apparent in the findings of one observer but not of the other. The only consistent and definite change seemed to be in edema of the stroma (and its obverse, density of the stroma). This, of course, would be a difficult criterion to use in estimating the stage of a cycle of a particular cervix.

The question may be raised as to the reason for the variations between the findings of the two observers. Part of the difference is due to the great variations in different parts of the same cervix. This is demonstrated in Figs. 2 to 5. It is obvious that the observers in tabulating their data on some of the criteria could well have used different portions of the cervix and thus have formed different impressions. Probably the most important reason is that for most of the criteria the judgment had to be based on impressions rather than actual objective measurable findings.

This is borne out by a further examination of the data. In Tables I, II, and III the third column in each instance shows the percentage of agreement between observers. This varied a great deal in the various criteria. The data for each criterion was analyzed statistically* to determine whether the agreement was real or due to chance.

The probability that the agreement was due to chance alone was negligible in ten of the criteria (less than five chances in 100). In nine cases, however, the agreement was most likely due solely to chance (more than five chances in 100). No analysis was made in three instances because of nearly complete agreement. However, it was obvious the standard (5 divisions on a micrometer ocular) for high columnar epithelium was unsatisfactory because nearly all the observations were placed above the standard. There may be some variation using a higher standard, therefore, our data are of no value regarding the height of the epithelium.

The only statistically significant† cyclic variation found with the use of the reliable criteria was, again, the edema of the stroma which appeared to be less during the late secretory phase.

B. Endometrial Hyperplasia.—The findings of the thirty cases studied are summarized in Table IV. The glands appeared to be more numerous and tortuous in the group of cervices from patients with endometrial hyperplasia when compared with the normal group. Nuclear size was measured with an ocular micrometer used with the high power (4 mm.) objective. The greatest diameter of twenty nuclei picked at random in the glandular epithelium of each cervix was measured. The average size of the nuclei in the normal group

*Tetrachoric method. Guilford, J. P.: Fundamental Statistics in Psychology and Education, New York, 1950, McGraw-Hill Book Company.

†Less than 0.01 by the chi square method. Ibid.

was 7.87 millimicrons (standard deviation 0.9231). The average in the hyperplasia group was 8.99 millimicrons (standard deviation 0.925). This small difference in the size of the nuclei, when analyzed statistically in a series of this magnitude, is very definitely significant (probably 0.01). However, this difference is not large enough to be used as a method of classifying an individual cervix.

TABLE IV*

	POST-MENOPAUSAL	"NORMAL"	ENDOMETRIAL HYPERPLASIA
Surface Epithelium.—			
Number of cases	14†	30	24†
High columnar	56	81	92
Secretion on surface	0	3	4
Nuclei, basal	89	73	84
Oval	100	81	96
Deeply stained	89	97	96
Glands.—			
Number of cases	15	30	30
Many glands	0	53	70
Simple glands	100	53	40
Narrow glands	70	53	43
Secretion in lumen	0	63	70
High columnar epith.	80	93	97
Cells distinct	70	77	87
Nuclei, basal	90	80	90
Oval	100	73	87
Large	10	Measured	
Deeply stained	90	100	97
Stroma.—			
Dense	60	60	73
Edema	30	40	37
Red blood cells	0	0	3
Nuclei, large	100	100	100
Deeply stained	100	100	100
Vessels, few	80	47	40
Collapsed	70	53	57

*Results expressed in percentages.

†Surface epithelium absent in some cases and unsuitable because of metaplasia in other cases.

The papillary projections described by Sjovall were observed in twenty-one specimens or 70 per cent (Table V). However, the projections were present in 30 per cent of the normal group and in 40 per cent of the cervices observed for possible cyclic variation. Thus it was felt that the papillary projections alone were not a reliable criterion in an individual cervix to justify a diagnosis of endometrial hyperplasia. In addition, the interpretation of papillary projections is difficult because the histological pattern is often confused with apparent projections which are really the result of the plane of section through branches of a racemose gland.

TABLE V. PAPILLARY PROJECTIONS

	NUMBER OF CASES	PROJECTIONS PRESENT	PER CENT
Endometrial hyperplasia	30	21	70
Control "normal" group	30	9	30
Early proliferative	11	6	55
Late proliferative	11	4	36
Early secretory	15	7	47
Late secretory	12	4	33
Menstrual	9	2	22

TABLE VI. EVALUATION OF CERVIX IN ROUTINE SPECIMENS

ENDOMETRIUM	CORRECT	INCORRECT
Proliferative	38	35
Secretory	35	45
Menstrual	3	17
Atrophic	23	4
Hyperplasia	4	2
Pregnancy	2	3
Subtotals	105	106
Total cases	211	

C. Postmenopausal or Senile Group.—The only finding which appeared to be of significance in the fifteen cervices examined in the postmenopausal group was the sparsity and simplicity of the glands. No other finding was considered to be useful with a given preparation.

D. Cervices From Routine Surgical Specimens.—A different approach was used as a final check. The cervix was examined in 211 cases from the routine surgical specimens without knowledge of the history or having seen other sections from the same case (Table VI). The cervix was classified as to the anticipated pattern of the endometrium or the stage of the cycle. Sections of the endometrium and, when available, the ovaries were then studied and the clinical history was noted. The results were almost evenly divided between the correct and incorrect interpretations. The greater accuracy in the atrophic phase was counterbalanced by the inaccuracy in the menstrual and late secretory phases.

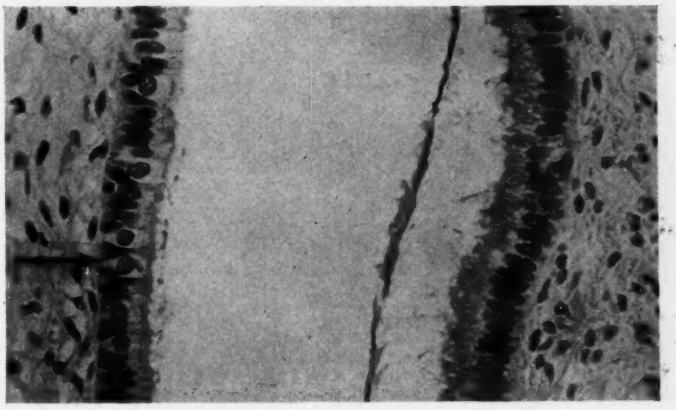

Fig. 1.—(No. 8514.) Example of the ciliated epithelium present in one endocervical gland. Note the ciliated cell. (×720.)

E. Miscellaneous.—A two-cell type epithelium with secretory or nonsecretory ciliated cells was observed in forty-nine cases, or 42 per cent of 118 cervices. However, no relation to the menstrual cycle was noted. The cilia were obvious in the better preparations without special stains (Fig. 1).

Metaplasia of varying degree was noted in fifty-seven, or 48 per cent, of the cervices. This incidence is lower than the 70 per cent found by Pund and Auerbach,[19] but agrees with the incidence of 40 per cent found by Carmichael and Jeaffreson.[20]

The paucity of mitotic figures in the endocervix was striking as they were found in only three cervices. More mitotic figures in at least some stages of the

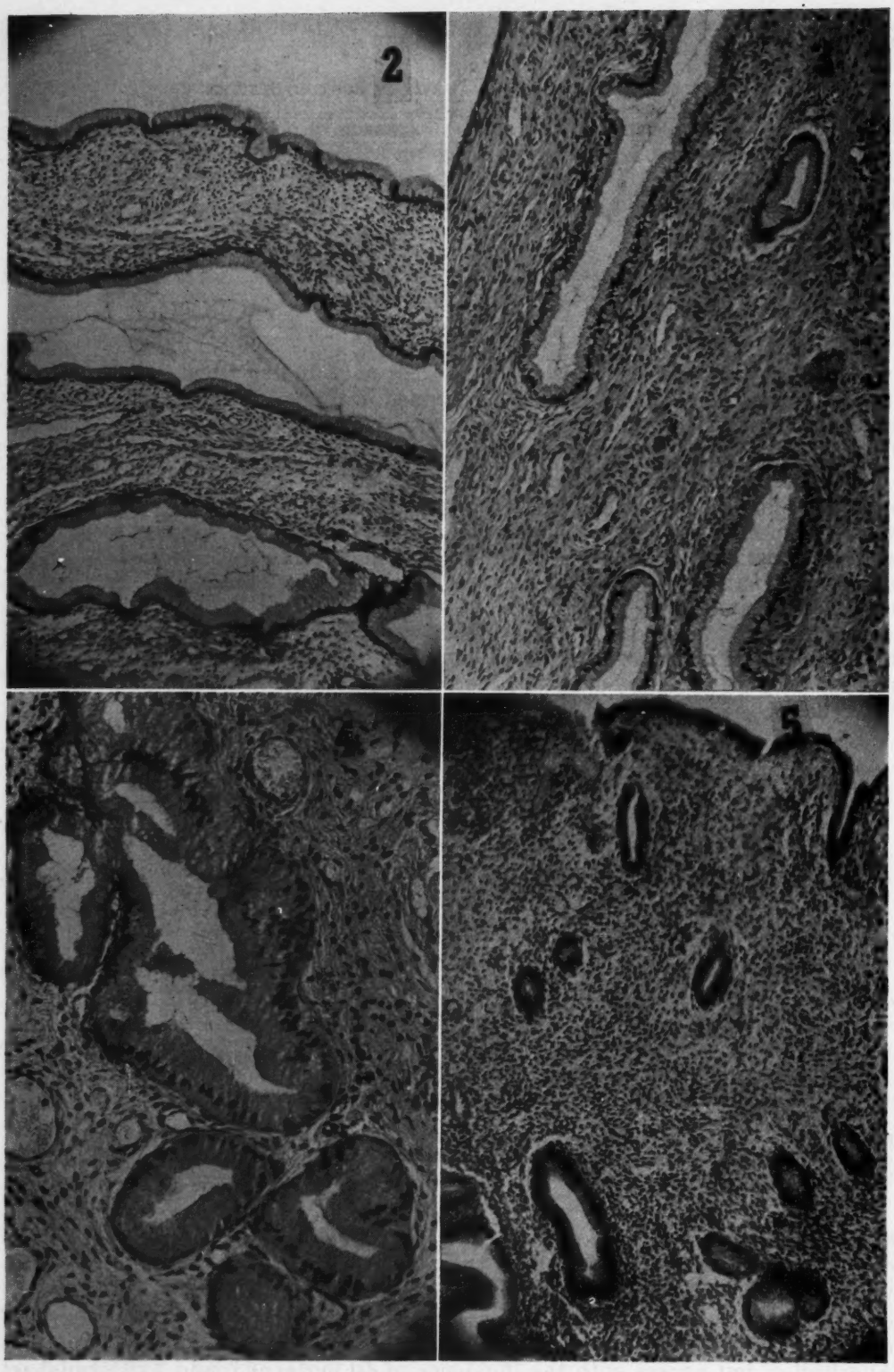

Fig. 2.—(No. 6130.) Endocervical glands which contain many of the criteria previously described by Wollner[2, 3, 4] for the late proliferative phase. (×200.)

Fig. 3.—(No. 6130.) Endocervical glands which contain changes described for the early secretory phase. (×200.)

Fig. 4.—(No. 6130.) Endocervical glands containing changes described for the late secretory phase. (×364.)

Fig. 5.—(No. 6130.) Proliferative endometrium from same case as Figs. 2, 3, and 4. (×200.)

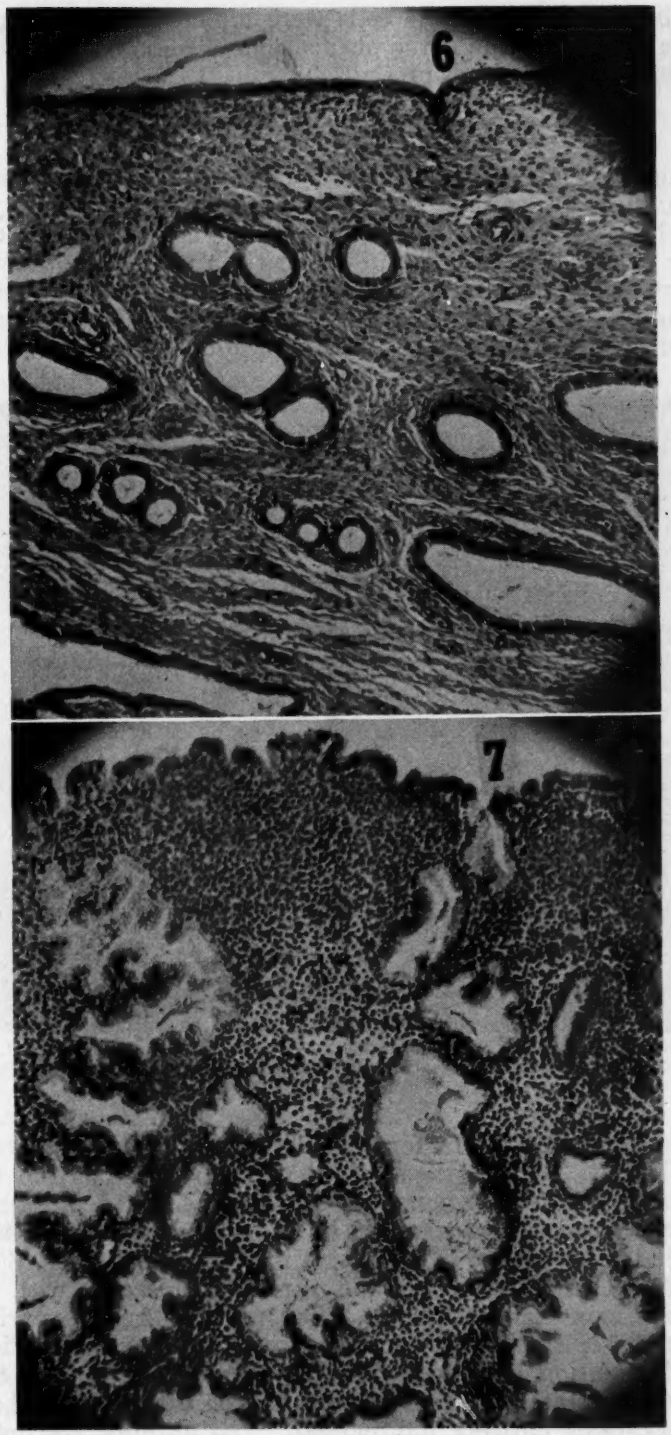

Fig. 6.—(No. 8073.) The endocervical glands which fit the description for the early proliferative phase. (×200.)

Fig. 7.—(No. 8073.) Secretory endometrium from same case as Fig. 6. Comparison of Figs. 6 and 7 with Figs 2, 3, 4, and 5 illustrates the difficulty in interpretation of a possible cycle in the endocervix. (×200.)

cycle would be anticipated if the cells were undergoing active cyclic growth. This would be especially true if the phenomenon of desquamation and regeneration at the menstrual period was present.

Comment

The changes during the menstrual cycle in the endometrium are definite and vary significantly so that with a given section it is usually possible to predict the phase of the cycle. However, in the endocervix we could find no such striking change. Only a few of the criteria previously described are objective enough to be reliable when utilized by two or more observers. It is obvious in interpreting individual slides that even the so-called reliable criteria are of no value in attempting to determine the phase of the cycle.

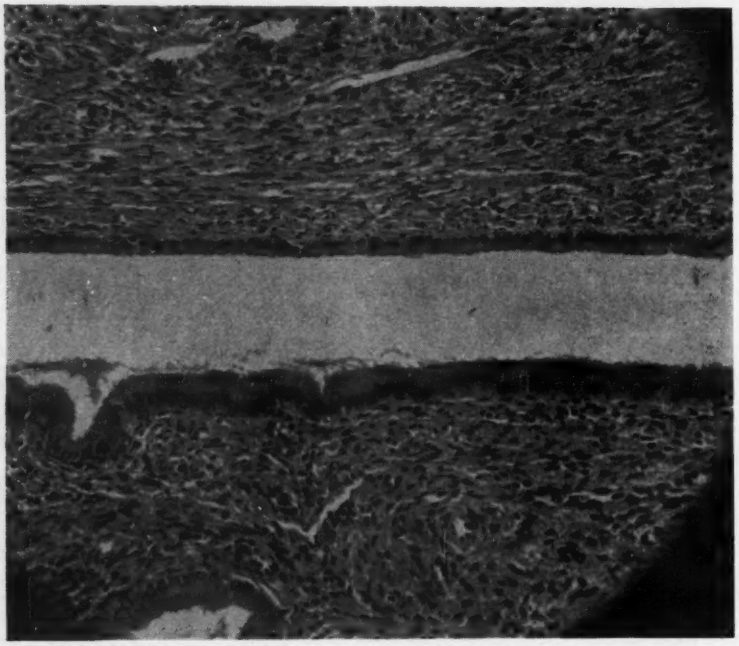

Fig. 8.—(No. 8090.) The variation in the epithelium of one endocervical gland is striking. (×200.)

There are many other factors which make the interpretation of the endocervix difficult. As previously stated, sections from the cervix often vary considerably in different portions. Figs. 2, 3, 4, and 5 illustrate the variation in the endocervical glands noted in one specimen. The difficulty in attempting to judge the phase of the cycle is apparent in Figs. 6 and 7. The appearance of the racemose type gland varies considerably with the plane of section of the cervix making interpretation unreliable. The variation of the appearance of the epithelium in one gland was often striking (Fig. 8). Some degree of inflammation is present in most cervices, adding to the difficulty of interpretation. Metaplasia of varying degree often alters the epithelium to make observations entirely impractical. The authors are impressed that there is variation in the histological pattern of the cervix, but, having tried to apply criteria advanced by others, have failed to demonstrate any constant cyclic change. Further, in the tabulating of all factors, no new evidence of constant or diagnostic significance has made itself apparent. Hormones

have long been linked with the changes of the endocervix, yet in the group of cervices with hyperplasia where this influence would be expected to be maximal there were no changes which were so characteristic of this condition as to be useful with a given preparation.

Summary and Conclusions

1. A brief review of the literature is presented.

2. A total of 344 cervices were studied. These include:

a. One hundred thirty-three studied for possible changes due to the phases of the menstrual cycle, the postmenopausal state, and endometrial hyperplasia.

b. Two hundred eleven studied as "unknowns" with an attempt to predict the phase of the menstrual cycle.

3. The findings demonstrated no clear cyclic changes in the human endocervix.

4. It was impossible to assess the stage of the cycle in a given cervix with an adequate degree of accuracy.

5. Only the paucity and simplicity of the glands were striking in the postmenopausal group.

6. The findings in the hyperplasia group were inconsistent and not sufficiently marked to be diagnostic in individual cervices.

The authors wish to express their thanks to Dr. B. M. Peckham for his invaluable aid in preparing the manuscript and helping with the statistical analysis of the data.

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Discussion

DR. M. C. WHEELOCK.—I enjoyed this paper very much for several reasons. In the first place, I think Dr. Bradburn and Dr. Webb did an amazing amount of work. Knowing that an investigation like Wollner's, when it was presented originally, may result in excessive

demands on our part in an attempt to utilize it in the future, makes me appreciate much more the realization that I will not have to look over a large number of endocervical biopsies and attempt to evaluate the stage of the cycle.

I wonder whether there was any pronounced change in stromal vascularization; if they emphasized it I did not catch it.

Did the cilia decrease in number or in relation to one another or in relationship to the cells? I raised this question as a matter of curiosity and not as it applies to the paper. I am glad to learn that we can continue to utilize the endometrium as a means of determining the status of the menstrual cycle.

DR. D. N. DANFORTH.—Dr. Bradburn and Dr. Webb have shown clearly and, to my judgment, with finality, that specific cyclic variations in the endocervical mucosa cannot be demonstrated in routine preparations. This finding is in agreement with my own limited observations in 25 cases. Of these, 15 were in the proliferative phase, 10 in the secretory. Variations in the same specimen were just as great as variations between different specimens.

One wonders at the enormous divergence of opinion by workers in this field. At the present time the burden of proof appears to rest upon those who insist that there is direct histological correlation of the endocervix with the ovarian cycle. It would greatly strengthen their case if they could agree whether the height of the response occurs in the proliferative, in the secretory phase, or during pregnancy.

The question arises whether more direct special stains and cytochemical studies might be productive. Since cyclic changes in the amount, viscosity, and composition of endocervical secretions have been demonstrated beyond question, it follows necessarily that there must also be changes in cellular activity. In four of the essayists' cases special stains gave no additional information. In four cases of my own these stains were also disappointing. Stains of the Golgi apparatus, which theoretically should be fruitful, have thus far not been illuminating. However, it is reasonable to hope that other stains and histochemical techniques will demonstrate the nature of the stimulus and the specific cellular response. In the meantime, Drs. Bradburn and Webb have done much to reduce this problem to its proper terms, and to clear the way for further study.

DR. BRADBURN (Closing).—In an effort to try to answer the question whether there are vascular changes that are not constant, a lot has to do with the clamping off the cervix at the time of surgery. Some vessels are filled with blood. There is no constant change. The cilia do not change particularly either.

Dr. Danforth mentioned again the cyclic changes in the cervical mucous secretion and the fact that there must be something causing them, and perhaps they may even come from the endometrium. Perhaps there is a hormone or an enzyme produced by endometrial gland secretion which may in some way or other alter the mucus that is present. I do not think that has been investigated. This is one possibility.

NUTRITION AND PREMATURE LABOR

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PREMATURITY is responsible each year for more than 60,000 lost lives in the United States and ranks first among the causes of neonatal death.[1] About 6 per cent of all viable births are premature, and the death rate for these infants is 26 times as high as for full-term babies, according to a recent report.[2] There are many recognized causes of premature labor. These include multiple pregnancy, toxemia, uterine tumors, other maternal diseases, placenta previa, premature separation of the placenta, abnormalities or death of the fetus, and trauma.[3] In about one-fifth of the cases, premature delivery is the direct result of obstetrical intervention, that is, induction of labor or cesarean section.[4] There still remains a large proportion, about one-third of the total cases, in which no cause for premature labor can be found.[5]

Within the past few years there has sprung up a belief that maternal nutritional inadequacy is primarily responsible for the premature onset of labor in this hitherto unexplained group to which no other cause could be assigned. The practical implications of this view are so far-reaching that it is important that all available evidence be scrutinized, either to provide further support for this concept or to check its growing acceptance. The present study has been designed to examine the problem through the following three approaches:

1. An analysis of the relevant literature;
2. An evaluation of the nutritional status of patients with premature labor by means of dietary histories;
3. An evaluation of the nutritional status of patients with premature labor by measurement of certain blood components.

The currently accepted criterion of prematurity is a birth weight of 2,500 grams or less. This factor, because of its greater accuracy and ease of measurement, has largely superseded body length of the newborn and estimation of the duration of pregnancy. The over-all advantage of this single criterion of prematurity is large. Patients are notoriously inaccurate in their recollection of the date of the last menstrual period. Many keep no records. A small proportion of women conceive while lactating and before the resumption of their menses, so that there is no last menstrual period from which to reckon. Finally, a significant number of gravidas experience physiologic bleeding in early pregnancy (Hartman's placental sign) which they mistake for a men-

strual period and which thereby vitiates calculations of the duration of gestation. The difficulties encountered in the accurate measurement of the length of a wriggling newborn infant are well known.

Although not as frequent, errors may also result from reliance on birth weight as the sole criterion of prematurity. Some diabetics, for example, may be delivered prematurely of babies of term weight, and women suffering from chronic vascular disease, or other severe chronic illness may produce tiny infants at full term. The concept of prematurity based on a birth weight of 2,500 grams or less cannot always be used interchangeably, therefore, with that of premature birth based on a gestation of less than 37 weeks. Nevertheless, a high correlation has been established between the duration of pregnancy and the birth weight of the infant, so that the great majority of all babies born prematurely weigh under 2,500 grams. Similarly almost all babies of greater than 37 weeks gestation age weigh more than 2,500 grams.

Review of Literature

Evidence from several sources has suggested a relation between economic privilege and premature labor. In the series at the New York Hospital[4] and at Johns Hopkins[6] the incidence of premature labor was twice as high among Negroes as among white patients. Inferences as to the economic significance of this disparity must be drawn with caution, however, since at the New York Hospital the incidence of premature labor was the same among white ward patients as among private patients. In a 15-year study of prematurity, which included 2,960 premature births, Tyson[7] could not prove that race or economic status were determining factors. In a more recent study of 13,257 premature births in England, Douglas[8] reported a low incidence of premature delivery among the most prosperous 9 per cent of the population but could detect no social class difference among the remaining 91 per cent. Douglas attributed the different incidence of premature labor in the 2 main groups to the amount of work required of the mother.

A widely quoted paper by Baird[9] purports to demonstrate the influence of social and economic factors on the incidence of premature labor in Scotland. In a series of patients who had enrolled for private care the incidence of premature labor was 4 per cent, whereas its incidence was 8.4 per cent, or more than doubled, among the registered ward clientele. Only 15 per cent of the cases of premature labor in the high-income group could not be explained on the basis of recognized obstetrical causes, whereas 52 per cent of the premature labors in the low-income group fell into this category. Baird suggested the most probable cause of these premature labors to be "poor health and nutrition of the mother." It may be pointed out, however, that the two groups of patients were inadequately controlled with respect to age, overwork, standard of obstetrical care, and other factors. Moreover, it is probable that at least some of the ward population had been "booked" because of the existence of abnormalities which in themselves predispose to premature labor. Further, eclamptic toxemia, the most common obstetrical condition associated with prematurity in Baird's experience, was twice as common among the poor as among the well-to-do. Perhaps more important is the point to which Barcroft[10] has called attention: In 19 per cent of the unexplained cases of prematurity among the ward patients, the pregnancy had reached 40 weeks, and in 34 per cent it had reached 38 weeks. In other words, one-third of the cases of unexplained prematurity did not result from premature labor. The infants,

because of their birth weights of less than 5½ pounds, were premature by definition, although the problem seemed to be primarily an interference with fetal growth. Baird's own observations offer a partial explanation for this. A significant relation exists between height of the mother and weight of the newborn. In the city of Glasgow there was a difference of about 3 inches in height between 2 groups of expectant mothers selected only on the basis of expense of confinement, the well-to-do being the taller. To ascribe their greater height, at least partly, to better nutrition would seem reasonable, but this growth effect must have been produced before closure of the epiphyses, an event usually remote from reproduction. Others[11] have also observed the tendency of small mothers to produce small offspring.

It is apparent, therefore, that complete agreement has not been reached concerning the importance of economic status as a factor in premature labor. Even if this premise be accepted, the idea that nutritional inadequacy in the underprivileged mother is responsible is still conjecture. Alternate possibilities exist. In one study,[11] for example, in which the patients were all from the same low economic stratum, the incidence of mothers who said they had insufficient rest during pregnancy and that their duties had been out of proportion to their capabilities was almost exactly twice as high among the women with premature babies as among those with full-term infants.

Several studies have correlated birth weight and changes in incidence of premature birth, on one hand, with the major reductions in national dietaries which resulted from World War II, on the other. In Austria, Husslein[12] reported a lowered average birth weight after the recent war and attributed this reduction to maternal malnutrition. Another study,[13] covering the years 1937-1948, was made in Wuppertal, Germany, by a unit of the British Medical Research Council. In 1945, when the food situation was said to be at its worst, there was a sharp reduction in the average birth weight. The children born during that year were 185 grams lighter than the average for 1937-1938, and in 1946 the birth weight rose again. The same study also reports, however, that in 1945, the average period of gestation was shortened by only 1.25 days, which would account for a reduction of only 45 grams in a normal child. The diminution in birth weight which occurred in 1945, although possibly related to faulty maternal nutrition, can scarcely be attributed to premature birth.

During the same winter (1944-1945) Stroink[14] recorded an increase in the prematurity rate to 8.6 per cent at the Utrecht University Clinic in Holland, from a normal of 4 per cent in 1939-1940. These rates, however, were based on a gestation of less than 38 weeks. In contrast to the reports from Germany the birth weight of the term infants was unaffected, despite a diminished maternal weight gain during pregnancy.

A more extensive study was made in Holland by Smith.[15] This careful analysis revealed a slight increase in the incidence of prematurity during the famine period but the difference was so small as to be of no statistical significance, according to the author.

During the siege of Leningrad in 1942, an increase in the incidence of premature births was observed by Antonov.[16] The particularly severe hunger during the first half of the year witnessed a premature birth rate of 41.2 per cent of all live births. Antonov's statistics are perforce incomplete and it has been impossible to evaluate factors other than food.

Reports from Finland[17] show an actual decrease in the incidence of premature birth during the war. At the Women's Clinic in Helsinki the incidence of premature delivery had remained relatively constant (10-12 per cent) between the years 1917 and 1942. In 1942, the premature birth rate fell to

about 6 per cent, where it remained throughout the war. This change occurred at the time when living conditions in Finland became much worse.

Population groups having different dietary habits have been compared with respect to incidence of premature birth. Some authors have professed to demonstrate in this manner a relation between dietary inadequacy and premature delivery. In certain widely quoted clinical experiments supplementation of the diet is believed to have resulted in a reduction in the premature birth rate.

One of the earliest of these studies was by Ebbs, Tisdall, and Scott.[18] They divided 400 pregnant women, all of low income, into 3 groups according to analysis of their diets. The first group (120 patients), with a poor diet, served as a control. The second group (90 patients), also with a poor diet, was given food supplements during the last 3 to 4 months of pregnancy. The third group (170 patients) had a moderately good diet, which was further improved by education. The incidence of premature delivery in Group 1 was 8 per cent, in Group 2, 2.2 per cent; in Group 3, 3 per cent. The last group is probably not strictly comparable with the first 2, because only 3 per cent of the women in it were on public welfare relief, in contrast to 44 per cent and 48 per cent of the women in the first 2 groups. The superiority of Group 2 over Group 1 is only apparent. The total numbers involved are small, and when these figures are subjected to simple statistical treatment the difference is found to be insignificant. Moreover, the incidence of toxemia was more than twice as great in Group 1 as in Group 2, and this difference in itself (although it too is not significant) would have been adequate to explain a higher premature rate in the former.

A similar and widely quoted study was reported in several papers by Mrs. Burke[19] and associates. This study was based on the dietary histories of 216 nonconsecutive selected patients who comprised a nonhomogeneous group. Correlation was made between nutritional ratings of the mothers and certain obstetric and pediatric data. A total of only 9 premature births occurred in the entire group, all of them to mothers whose diets were judged inadequate. The total number of mothers in this category, however, is not stated. The mothers of three of these premature infants were enrolled in the study by special request, because of the pediatrician's interest in prematurity. Among the entire group of 216 patients, 10 pregnancies were terminated artificially and it is not clear whether any of the premature births resulted from this obstetrical intervention. The incidence of pre-eclampsia was 44 per cent in the women with poor or very poor diets, 0 per cent in those with good or excellent diets. A real difference between the 2 groups in the incidence of premature labor could be explained on the basis of this great difference in incidence of toxemia. It appears doubtful, however, that the conclusions concerning prematurity are statistically valid. In addition to the criticisms already mentioned, the total number of cases appears too small. The complete absence of premature births from the group with good or excellent diets would in itself attest the inadequacy of the sample.

The People's League of Health studied the dietary records of 5,022 women in 10 hospitals in London and issued 3 reports on their findings. Although the standards were not mentioned, widespread deficiencies were judged to exist with respect to intake of calcium, iron, and vitamins A, B, and C. Daily supplements which included these essentials were therefore given to alternate patients during pregnancy, 2,510 expectant mothers receiving the supplement, 2,512 serving as controls. The Committee classified as premature all deliveries which occurred *before the fortieth week.* With this criterion the incidence of prematurity was higher among the controls (24.0 per cent) than in the treated

group (20.1 per cent). These figures, however, are not indicative of a real difference in the incidence of prematurity based on the more generally accepted criterion of birth weight. The average weight of the offspring of treated primiparas was 7.18 ± 0.03 pounds; that of the control infants, 7.17 ± 0.03 pounds. The difference for the offspring of multiparas was similarly insignificant. Further evidence of the absence of a significant difference in the prematurity rates is provided by the infant mortality data. Although the Registrar-General has reported that 50 per cent of all infantile deaths under 1 month are due to prematurity, practically identical infant mortality rates (including stillbirths and neonatal deaths) existed in the 2 groups.

A well-controlled study by Dieckmann and others[21] of 553 patients of a low-income group showed that dietary supplements of calcium, phosphorus, iron, and vitamins A and D had no effect on the duration of pregnancy nor on the weight of the offspring.

Toverud[22] has recently reported on the obstetrical experience of a health station which served a section of Oslo during the last war and which provided close prenatal supervision and dietary supplements for its patients. The incidence of premature birth among 728 deliveries was 2.2 per cent, as compared with 4.6 per cent among 2,391 deliveries for all of Oslo. This difference is barely significant statistically, but it is questionable whether the two population groups are comparable from the standpoint of nondietary factors.

A remarkable report was made from the Philadelphia Lying-In Hospital by Tompkins[23] in 1941. A group of 750 obstetrical patients was given special dietary instruction, including supplementary vitamins. *No premature births* occurred in this group, a birth weight of 5 pounds or less being the criterion of prematurity. The premature birth rate for the hospital was 4.93 per cent. This report also states that signs and/or symptoms of nutritional deficiency existed in *82 per cent* of the clinic's patients.

A later report by the same author[24] presents data at variance with the above. His more recent study group, comprising 593 patients, had a premature birth rate of 4.16 per cent, in contrast to a rate of 7.07 per cent for the controls (772 patients). The nature of the controls in this report is not made clear, but it is interesting that the prematurity rate is increased 43 per cent above the earlier control figure.

In what appears to be one of the best-controlled studies yet reported, Cameron and Graham[25] have obtained evidence of the influence of antenatal diet on prematurity. The diets of 100 women who had had premature deliveries were compared with those of 100 women with term deliveries. Although only average values are given, the mothers of the full-term infants had distinctly higher calculated intakes of fat, protein, calcium, phosphorus, and iron. In the second part of this study 500 alternate patients were subjected to very careful supervision of diet and food supplementation, an equal number of alternate patients serving as controls. An advantage of borderline statistical significance accrued to the former. The supervised patients had a premature rate of 6.2 per cent as compared with 10 per cent for the controls. The patients in this study were mostly from a low economic level. The obstetrical and medical causes of premature labor were not taken into account. It seems at least possible that a diminished food intake among the mothers of the prematures in the first part of the study may have resulted from chronic illnesses which in themselves might have been factors in the causation of premature labor. The report fails to exclude pregnancies which might have been terminated prematurely through obstetrical intervention, such as induction of labor or cesarean section. If poor nutrition predisposes to toxemia, as has been alleged in several recent reports, it is conceivable that the premature delivery rate in

the control group may have been increased indirectly by it, through the artificial termination of pregnancy in the treatment of toxemia. Finally, in the comparison of two groups, only one of which has received very close supervision, one must consider the possible effect of factors other than the specific one under study. The possible importance of psychologic factors cannot be excluded.

Protein is the specific dietary factor which has been the subject of greatest interest in relation to prematurity. In the rat, nutritional impoverishment of the fetus can be produced by maintenance of the mother on a nitrogen-free diet during pregnancy.[26] This severe dietary restriction results primarily in interference with fetal growth rather than in premature labor. In one of the papers published by Mrs. Burke and her associates in Boston, based on the same 216 mothers previously described, the conclusion was reached that the amount of protein in the mother's diet had the greatest effect on the incidence of prematurity because of the demonstrated relation of maternal protein intake to the birth weight and length of the newborn. Some of the criticisms of this work have already been mentioned. Sontag and Wines[27] were not only unable to confirm these findings in their dietary study of 205 mothers, but they further criticized the Boston study because some of the premature babies in it were born to mothers with toxemia who had been put on low-protein diets therapeutically.

In an earlier study of 514 women, Williams and Fralin[28] found the average protein intake of the patients with unexplained premature labor to be almost identical with that of the rest of the group. In another carefully controlled study of 1,400 private patients, Holmes[29] had found the incidence of premature labor only half as high in the low-protein group (60-70 grams daily) as in the high-protein group (110-120 grams daily). These reports offer no support to the view that protein deficiency results in premature labor.

A suggestion that riboflavin deficiency may be a factor in the causation of premature labor was made in a report from Palestine by Brzezinski and others.[30] In a study of 326 pregnant women the incidence of premature delivery was more than twice as high (14.6 per cent versus 5.5 per cent) in the group of 122 with depressed riboflavin excretion as in the 204 patients whose excretion of the vitamin more nearly approached the norm for the region.

Present Study

The foregoing literature fails to prove conclusively that premature labor in the human being results from inadequate maternal nutrition. The present study was designed to provide data to test this hypothesis. Included in the study were 70 mothers of liveborn premature infants (birth weight of 2,500 grams or less) and 67 control mothers of term infants (birth weight over 2,500 grams). Only those premature births were included in which no recognized cause of premature labor was present. This excluded multiple pregnancies, induced labors, cesarean sections, placenta previa, premature separation of the placenta, toxemia, fetal death in utero, and fetal malformations. Premature rupture of the membranes did not exclude a patient from the study, since this is believed often to be the result rather than the cause of the processes leading to the onset of labor. The control patients were selected at random, concurrently with the prematures, from a large group who had undergone normal pregnancies and deliveries at term. All patients were from the ward service of the Sloane Hospital for Women and were delivered during the years 1948 and 1949.

Of the patients with premature labors 47 were white and 22 were Negro. Thirty-eight of the control patients were white and 32 Negro. In the former group there were 32 primiparas, as compared with 28 among the controls. The

differences in average maternal age, height, and postpartum weight were insignificant. These data are summarized in Table I. The average maternal weight before delivery, however, was 8 pounds greater in the control patients. This difference is readily explained by the shorter duration of prematurely terminated pregnancies. The average weight of the newborn in the premature series was 1,900 grams (range 580-2,490 grams), as compared with an average birth weight of 3,320 grams (range 2,520-4,110 grams) in the control series. Routine antenatal care in the outpatient department included a lecture by one of the hospital dieticians on basic dietetics, but no food or vitamin supplements were supplied.

TABLE I. MATERNAL AGE, HEIGHT, AND WEIGHT

	PREMATURES	TERM CONTROLS
Age (years)	26.8 (19-45)	27.5 (18-41)
Height (inches)	63 (56 5-69.0)	62.4 (54-67.5)
Weight (term) (pounds)	140 (110-176)	148 (110-201)
Weight (pounds) (Fourth day post partum)	132 (110-160)	131 (99-170)

By the selection of patients for study after the completion of pregnancy it has been possible to effect a great economy of labor. Approximately one-third of all premature labors are of unknown cause. During the years 1948 and 1949 premature births comprised 9 per cent of all viable births on the ward service. Therefore, if study of our patients had been begun during the antenatal period, it would have been necessary to include approximately 2,300 women in order to provide the 70 cases of premature labor in our study. The latter type of approach affords the theoretical advantage, however, of providing data on outcome of pregnancy for a fixed population group, whereas an unknown and variable part may be lost to study in a retrospective investigation because of discontinued attendance during pregnancy or abortion.

The study consisted of two parts: a dietary interrogation and analysis (80 patients), and the measurement of certain blood components related to nutrition (107 patients). Most of the subjects were included in both parts of the study. The dietary history was obtained during the patient's postpartum stay in the hospital, by a trained dietician who was unaware of the duration of the pregnancy and the weight of the baby. Approximately an hour and a half were spent with each patient, during which time the various foods and amounts eaten during an average week were tabulated in detail. These data were recorded on special forms prepared for this purpose. With the aid of a standard table,[31] calculation was then made of the average daily intake of calories, protein, fat, carbohydrate, calcium, iron, vitamin A, thiamine, riboflavin, niacin, and ascorbic acid.

A summary of the dietary analyses is presented in Table II, together with the nutritional allowances for pregnancy, as recommended by the Food and Nutrition Board of the National Research Council. The average daily carbohydrate consumption was identical for the control mothers and the mothers of premature babies. The control averages were slightly higher for each of the other nutritional components, but in no instance was the difference statistically significant. The general adequacy of the average dietary values, for both controls and premature mothers, is attested by their good agreement with the recommended allowances. Subject to the shortcomings of this method of study, discussed later, these observations fail to demonstrate a significant difference in food consumption between women who went into labor prematurely and women whose pregnancies continued to term. The diet of the population under study conformed well with the current dietary recommendations for pregnant women.

TABLE II. AVERAGE DAILY FOOD INTAKE DURING PREGNANCY

	PREMATURES	CONTROLS	RECOMMENDED*
Calories	2,455 (1,005-3,525)	2,520 (1,710-3,995)	2,500
Protein, Gm.	83 (46-124)	91 (47-140)	85
Fat, Gm.	113 (39-176)	117 (60-203)	
Carbohydrate, Gm.	287 (115-449)	287 (163-385)	
Calcium, mg.	1,220 (420-2,570)	1,430 (270-2,810)	1,500
Iron, mg.	13.1 (6.5-21.1)	14.2 (8.1-18.7)	15
Vitamin A, I.U.	6,098 (903-16,908)	6,700 (1,873-12,175)	6,000
Thiamine, mg.	1.2 (0.5-1.7)	1.5 (0.7-3.2)	1.8
Niacin, mg.	10.8 (6.5-15.3)	11.6 (6.3-18.2)	18
Riboflavin, mg.	2.4 (1.0-5.8)	2.7 (0.9-4.8)	2.5
Ascorbic Acid, mg.	100 (16-209)	112 (16-214)	100

*Food and Nutrition Board, National Research Council, 1945.

Biochemical and hematological determinations were performed in duplicate on blood obtained by venipuncture on the first workday following delivery, usually within 24 hours. None of the patients had suffered postpartum hemorrhage and none had been transfused. Studies included serum proteins, serum amino acid nitrogen, hematocrit, hemoglobin, serum alkaline phosphatase, serum vitamin A, serum carotene, serum ascorbic acid, and whole blood ascorbic acid. Serum protein determination was made by the direct Kjeldahl method and titration. Amino acid nitrogen was determined with beta-naphthoquinone-4-sulfonic acid, as described by Folin and modified by Danielson.[32] Hemoglobin determination was made by direct photometry of an alkaline solution. Alkaline phosphatase was determined by the method of Bodansky.[33] The method of Bessey and associates[34] was used for vitamin A and carotene; and ascorbic acid was measured by the method of Roe and Kuether.[35]

TABLE III. AVERAGE VALUES OF BLOOD COMPONENTS FOLLOWING DELIVERY

	PREMATURES	CONTROLS	SATISFACTORY MINIMUM
Serum proteins (Gm./100 c.c.)	6.1 (5.0-7.3)	5.9 (5.1-7.4)	5.5
Serum amino acid nitrogen (mg./100 c.c.)	5.5 (3.6-7.7)	5.4 (3.9-7.7)	5.0
Red cell volume (hematocrit)	36.8 (27.5-48.0)	35.8 (27.0-46.4)	34.0
Hemoglobin (Gm./100 c.c.)	11.7 (8.8-14.6)	11.4 (8.2-14.4)	11.0
Serum alkaline phosphatase (Bodansky units)	5.0 (1.2-9.3)	5.5 (3.5-10.4)	See Ref. 36.
Serum vitamin A (U.S.P. units/100 c.c.)	54.3 (11.4-114.6)	53.5 (14.0-95.5)	50
Serum carotene (γ/100 c.c.)	191 (33.6-489)	182 (73.4-268)	100
Serum ascorbic acid (mg./100 c.c.)	0.57 (0.13-1.06)	0.67 (0.13-1.10)	0.4
Whole blood ascorbic acid (mg./100 c.c.)	0.74 (0.30-1.22)	0.85 (0.26-1.54)	

None of the differences between premature mothers and controls were statistically significant. The control levels were slightly higher for alkaline phosphatase and ascorbic acid; the premature figures were slightly higher for serum proteins, amino acid nitrogen, hematocrit, hemoglobin, vitamin A, and carotene. The alkaline phosphatase level, which increases in the serum as a result of deficiency of either vitamin D or calcium, normally undergoes a progressive rise during pregnancy also. Higher values are to be expected at full term,

therefore, than earlier in gestation.[36] The hemodilution of pregnancy, on the other hand, normally produces slightly lower levels of serum proteins, hematocrit, and hemoglobin. The average values for both groups showed good agreement with satisfactory minimum standards. For whatever value these blood components have as indicators of nutritional status, they lend no support to the view that maternal nutritional inadequacy is an important factor in the etiology of premature labor in this population.

Comment

So important has nutrition proved for so many physiologic functions that it is only natural that a possible nutritional basis be sought for hitherto unexplained malfunctions. The view concerning maternal nutrition expressed by the Royal College of Obstetricians and Gynecologists[37] in 1944 seems so reasonable that it has been incorporated into obstetric teaching and finds frequent expression as accepted fact in the current literature.[38] This Report stated, "There is a natural and physiologic basis for the view that the mother's nutrition exerts a major influence on the well-being of the unborn child and that any interference with the adequacy of her nutrition at a time when extra demands are being made upon it by the growing child is liable to increase the risk of prematurity and abortion." Despite the plausibility of this statement, convincing evidence is lacking that faulty maternal nutrition bears any direct relation to premature labor in the human being.

The adequacy of the controls for the association of poor maternal diet with premature labor is questionable. The nature of the relation, if indeed valid, is unknown. It has been conjectured[39] that a uterus which is poorly developed because of deficient diet cannot enlarge adequately to accommodate the products of conception. Women may eat poorly because of a multiplicity of reasons. These include poverty, ignorance, vanity, physical disease, and antipathies of psychological origin. All of these factors, and perhaps others as well, must be considered before one can properly ascribe premature labor directly to poor nutrition.

Methods for assessing state of nutrition in the human being are notoriously unsatisfactory. Dietary analysis, one method in common use and a part of this study, requires much time and effort and yields, at best, inexact results. Size of servings can be estimated only roughly unless actual measurements are made. Food composition varies according to season of year and geographic location. Variable losses occur during processing, transportation, and cooking. Added to this are the physiologic variables of digestion, absorption, utilization, excretion, and the varying physiologic demands which result from changing physiologic and pathologic states.[40] These limitations greatly restrict the value of the dietary standards for assessing the nutrition of individuals.

The interpretation of blood biochemical and hematological values in the light of their nutritional significance is beset with some of the same difficulties. Only partial correlation has been possible between these factors and dietary history. The dietary and blood standards possess the properties of a mean.[41] Because of this their usefulness in group studies is greatly enhanced over their significance for individuals. Despite their shortcomings they comprise the best available criteria for the assessment of nutrition in the absence of clinically apparent deficiency syndromes. In a controlled experiment significant differences between two groups would be expected to show themselves in such data.

That nutrition is a factor in premature labor is undisputed. All physiologic functions are dependent, at least indirectly, on nutrition. The issue is whether inadequate maternal nutrition bears a specific causal relation to pre-

mature labor, in the same sense as does infection, for example. A growing body of literature is aligned predominantly but not unanimously on the affirmative side of the question. The evidence to support this thesis appears incomplete, however, and fails to justify its acceptance.

The specific nutrients investigated in the present study, while not complete, cover a sufficiently wide range to permit an appraisal of group nutritional status. Two main facts have evolved. First, the nutrition of the premature parturients, as measured by dietary history and by hematological and biochemical determinations, showed good agreement with the accepted standards for pregnancy. Second, no significant differences existed between the mothers of premature infants and the full-term controls with respect to these same nutritional factors. Our findings therefore lend no support to the theory that maternal nutritional inadequacy is an important cause of premature labor.

Summary

1. The literature dealing with the relation of maternal nutrition to premature labor has been reviewed. Despite the prevailing view that nutritional inadequacy is a common cause of premature labor, the evidence for this is not convincing.

2. Dietary histories of a group of patients who had premature labors revealed no significant differences from those of a control group with full-term pregnancies in calculated intake of the various food essentials.

3. Hematological and blood biochemical determinations in the early puerperium also failed to reveal any significant differences between the premature parturients and their full-term controls. Determinations included serum proteins, serum amino acid nitrogen, red cell volume, hemoglobin, serum alkaline phosphatase, serum vitamin A, serum carotene, serum ascorbic acid, and whole blood ascorbic acid.

4. This study offers no support to the theory that nutritional deficiency is a common cause of premature labor.

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RETINAL CHANGES IN THE TOXEMIAS OF PREGNANCY

I. History, Vomiting of Pregnancy, Mild and Severe Pre-eclampsia, and Eclampsia*

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THE etiological factors responsible for the toxemias of pregnancy have not been revealed despite extensive researches during the past century. Most workers in this problem agree that the maternal vascular bed is extensively involved in this condition. Because of these changes, either gradual or sudden, in the arteriolar system, many of the symptoms and findings of toxemia make their appearance. The vessels may be readily observed by direct visualization of the fundi oculi. Since the New York Lying-In Hospital opened at its present location in 1932, a careful examination of the retinal vascular findings in all patients with toxemia has been recorded. This was possible because of close collaboration between the departments of Obstetrics and Ophthalmology. The purpose of this communication is to review these observations and correlate them with the other findings in the toxemias. Some of the more pertinent reports concerning retinal abnormalities in the toxemias, present standards for retinal changes, and the classification of the toxemias will be briefly reviewed. It is hoped that certain refinements in the management of the toxemias may result following the evaluation of these data.

History

Soon after the invention of the ophthalmoscope by Helmholtz, Albrecht von Graefe,[1] in 1855, described the first case of retinopathy with retinal detachment. Silex,[2] in 1895, reported 35 cases of advanced retinal changes in pregnancy. Schiotz,[3] in 1921, found 40 cases of retinopathy associated with pregnancy in an extensive survey of 8,400 women at the Christiania Clinic. The fetal mortality associated with retinopathy was as high as 80 per cent. Rochon-DuVigneaud[4] showed that uninterrupted pregnancy associated with retinopathy resulted in blindness or serious visual damage in 75 per cent of the cases. The great majority of the earlier authors associated retinopathy with a latent or an actual nephritis. Miller,[5] in 1915, went so far as to say that the presence of retinopathy was an important diagnostic factor suggesting the presence of nephritis. To Zangemeister,[6] "albuminuric retinitis" always indicated nephritis. Wolff and Zade[7] evaluated 13 cases clinically with advanced retinal changes; 10 were considered chronic nephritis. Cheney,[8] in 1924, reviewing the previous experience as well as his own, believed that 4 out of 5 cases of retinopathy were associated with nephritis. The above reports undoubtedly

*This work was supported by a grant from the James Foundation of New York, Inc.

referred to what we now designate as Grade III and IV retinal changes and indicate very advanced vascular changes. At present these findings are less frequently encountered because of better prenatal care and patients with serious malignant hypertension and advanced renal disease have been advised against pregnancy or have had the pregnancy interrupted.

During the past two decades the much more frequently encountered retinal changes classified as Grades I and II have been recognized and reported. Haselhorst and Mylius,[9] in 1928, and Masters[10] and Hallum[11] later in this country recognized marked retinal spasm which was at times transient or persistent, localized or diffuse. They associated this with severe toxemia and the arterial spasm was found to antedate retinopathy. After the pregnancy the spasm disappeared in many cases. Masters[10] in 1933 found a passive congestion of the retinal veins in the early months of pregnancy. He noted arteriolar spasm in most toxemias with a systolic blood pressure over 150 mm. Hg, and in only several was spasm noted with a blood pressure below 150. There was a rather close correlation between blood pressure elevation and retinal arteriolar spasm.

Mussey and Mundell,[12] in 1939, concluded that persistent arteriolar spasm was a guide to the further management of the toxemias. These authors found varying retinal changes with similar blood pressure and in 44 per cent of toxemia cases the progressive retinal vessel spasm was the deciding factor in the decision to terminate pregnancy. In others with a blood pressure of 150 to 200 systolic, the absence of retinal vascular change influenced the authors to take a more conservative attitude. Similarly, the retina indicated many times the difference between acute changes and changes which antedated the pregnancy. This was important from the point of view of diagnosis as well as of immediate therapeutic value.

Wagener and Keith,[14] in 1939, further stressed the importance of arteriolar retinal spasm as distinguished from true retinopathy. They stated that diffuse angiospasm may produce sufficient vascular injury to contraindicate further pregnancy and eventually result in permanent vascular disease. Wagener[15] pointed out in 1933 that the observed retinal lesions were nonspecific and could not be classified by ophthalmological examination into any of the types of toxemia. These observers believed that "albuminuric retinitis" was more often the result of diffuse arteriolar disease rather than primary glomerulonephritis. No definite correlation was found between the retinal arteriolar spasm and the blood pressure.

Recently Hallum[11] has emphasized the importance of the retinal examination in the toxemias of pregnancy. He believed that the degree of retinal change followed the course of the toxemias more accurately than any other single clinical sign or laboratory test. Early routine retinoscopy to establish the normal base line was advocated to compare the initial findings with those of a possible future toxemia. He found the retinal vascular changes in toxemia to be reliable guides in determining whether the pregnancy should be interrupted. In pre-eclampsia the degree of localized and generalized spasm paralleled the severity of the toxemia. This author stated that the arteriolar retinal changes were a direct reflection of similar processes occurring throughout the rest of the body. When frequent careful retinoscopy revealed increasing angiospasm he suggested interruption of the pregnancy. Wagener,[14] Schiotz,[3] Masters,[10] and Hallum[11] all agree that retinopathy may be a definite indication for interruption of the pregnancy. These authors find that when hemorrhages or exudates develop prior to the twenty-eighth week and the patient is allowed to continue to term, the possibility of permanent loss of some vision and future serious cardiovascular renal disease is great. Under these circumstances the infant has only a 25 per cent chance of survival.

The term "albuminuric retinitis" was coined by Liebreich[16] in 1859 to describe the retinal findings in nephritis. As pointed out by Fishberg and Oppenheimer,[17] the term should be discarded. The retinal lesions are not related to albuminuria and at times are most extensive with a complete absence of albuminuria. The fundamental fact about retinal change is that it is associated with arterial hypertension. In the few patients who do not have increased pressure the retinal findings are a residual from previous elevations. According to Wagener, Clay, and Gipner,[18] the component elements of these retinal changes are basically identical in all forms of renal and hypertensive disease. The lesions of the retina are not inflammatory but are the result of circulatory disturbances. The term retinopathy, referring to involvement of the retina by serous or hemorrhagic effusions, is preferable to the incorrect term "retinitis."

What is responsible for the retinal changes in the toxemias? Hypertension is the single physical sign which most frequently accompanies the changes in the retinal vessels. Volhard[19] advanced the theory that the retinal lesions may result from ischemia. Severe spasm with obliteration of the arteriolar lumen will produce vascular damage. Haselhorst and Mylius,[9] in 1928, observed the spasm of the retinal vessels in a case of eclampsia. At first they observed cramplike contractions for varying intervals along the arteries. Several days later spasms remained constant and involved longer stretches. The retina showed circumscribed, indistinctly limited, transparent, glassy, whitish-yellow lesions midway between the larger arterial branches. Diffuse edema occurred at the macula and vision became impaired. A cesarean section was performed and the patient rapidly improved. This was the first clearly illustrated change from retinal arteriolar spasm to true retinopathy and recovery, which lends support to Volhard's theory.

Although most authors have praised the additional knowledge obtained by ophthalmoscopy, Dieckmann and Brown,[13] in 1938, stated that a retinal examination, even though made by an experienced ophthalmologist, has been of little value in the toxemias of pregnancy either as to diagnosis or prognosis.

The reports of retinal hemorrhage associated with vomiting of pregnancy are rare. Although visual symptoms such as haziness, dimness of vision, and blurring are not uncommon, very few of such complaints have been found with observed retinal changes. Erismann[20] (Table I), in 1890, described the first case of vomiting of pregnancy associated with retinal hemorrhage. The patient died 5 days after admission. Kuhne,[21] in 1899, described a second case and the disaster was repeated. Wallick,[22] in 1909, at the Baudeloque Clinic, and Albeck,[23] in 1918, interrupted cases associated with known retinal hemorrhages; both patients lived. In 1932 Stander[24] first described in this country two cases with multiple retinal hemorrhages. In one case blurring of vision and eye hemorrhages occurred in the fifth month of gravidity. The pregnancy was allowed to continue and maternal death followed 9 days later. The second case occurred in the fourth month of pregnancy and was terminated immediately. The retinal hemorrhages disappeared in two weeks and the patient fully recovered. Stander concluded that retinal hemorrhage associated with vomiting of pregnancy is of grave prognostic significance and is an indication for therapeutic abortion. In the same year Tillman[25] reported 3 cases, all of which were interrupted, with 2 maternal deaths. Blurring of vision and diplopia preceded the retinal hemorrhages. Two cases were associated with renal disease, pyelonephritis, and cortical necrosis; the third patient, who was the only one to survive, developed a flaccid paralysis of the lower extremities. Tillman believed that the retinal hemorrhages were not specific and may have represented any variety of conditions from typhus and encephalitis to phos-

gene poisoning. In 1936 DeCarle[26] interrupted another case but maternal death followed. Schjott-Rivers[27] reported from the University Clinic in Oslo on the visual disturbances associated with vomiting of pregnancy over a 16-year period ending in 1937. During that time there were 3 cases with retinal hemorrhages. All 3 pregnancies were interrupted; all 3 patients died. Schjott-Rivers believed that ophthalmoscopic examination is necessary in any protracted case of vomiting of pregnancy. The occurrence of visual disturbances, with or without fundal changes, is an extremely serious prognostic sign. Waterman,[28] in 1939, described a single case of hyperemesis gravidarum with retinal hemorrhages which was interrupted, but maternal death followed. Ballantyne,[29] in 1941, described 6 cases of hyperemesis gravidarum with ocular complications, 2 of which were associated with retinal hemorrhage. This author found that early blurring of vision was associated with a retrobulbar neuritis manifested by a central visual field defect without visible ophthalmoscopic change. When the visual field defect was present alone, temporizing was sufficient. According to Ballantyne, if retinal hemorrhages occurred, however, immediate interruption was indicated. Evans and Kannapel[30] in 1949 reported one case of retinal hemorrhage in which prompt emptying of the uterus resulted in maternal recovery.

TABLE I. RETINAL HEMORRHAGE IN VOMITING OF PREGNANCY

AUTHOR	YEAR	INTERRUPTED PREGNANCY	MATERNAL OUTCOME
Erismann	1890	No	Died
Kuhne	1899	No	Died
Wallick	1909	Yes	Lived
Albeck	1918	Yes	Lived
Stander	1932	No	Died
Stander	1932	Yes	Lived
Tillman	1932	Yes	Died
Tillman	1932	Yes	Died
Tillman	1932	Yes	Lived
DeCarle	1936	Yes	Died
Schjott-Rivers	1938	Yes	Died
Schjott-Rivers	1938	Yes	Died
Schjott-Rivers	1938	Yes	Died
Waterman	1939	Yes	Died
Ballantyne	1941	Yes	Lived
Ballantyne	1941	Yes	Died
Evans	1949	Yes	Lived

In 1947 Wagener, Clay, and Gipner,[18] comprising a committee for the American Ophthalmological Society, submitted a joint report designed to standardize the classification of hypertensive disease of the retina. They stated that the component elements of retinopathy are basically identical in all forms of hypertensive and renal disease. The stages of retinal change (Table II) used in this study retain the same nomenclature as that of the committee and are simplified for particular use in the toxemias of pregnancy. Grade O is used to indicate normal retinal vascular findings. Grades I and II refer to different degrees of 3 distinct types of alteration which may occur in the retinal arterioles in different phases of hypertensive disease, which include generalized narrowing (probably representing increased tone), sclerosis (arteriolar thickening), and focal spasm. Grade I refers to the milder forms of these changes and Grade II may be applied to the more advanced forms under the same headings. Grade III includes, in addition, retinopathy which is defined by the committee as the abrupt development of serous and hemorrhagic extravasations into and under the retina. The serous edema may be

described as diffuse edema or "cotton wool" patches. Grade IV includes the further development of papilledema which is also termed neuroretinopathy. This grading of retinal findings is essential for diagnostic and prognostic evaluation. The grading gives an immediate simplified method of describing the severity of the retinal changes which are nonspecific, and practically identical lesions may occur in essential hypertension, nephritis, and the acute toxemias of pregnancy.

The complete bedside study of the retinal vessels is possible only after the dilation of the pupil. The mydriatics commonly used are homatropine, 1 per cent; eucatropine, 5 per cent; and phenylephrine (Neo-Synephrine), 10 per cent. A period of at least one-half hour is necessary before adequate dilation has resulted. After visualization of the fundi 1 per cent pilocarpine is instilled.

TABLE II. RETINAL ARTERIOLAR SIGNS

Grade I		Grade II
Slight	Reflex stripe Transulcency Arteriovenous phenomena Spasm	Moderate
Grade III		Grade IV
Edema Hemorrhage Transudate		Papilledema

Material

All cases with retinal examinations were grouped according to the toxemia classification of the American Committee on Maternal Welfare published in 1940. The type of toxemia (Table III) was decided upon by the duration[31] (before, during, and after pregnancy) of the blood pressure elevation, albuminuria, edema and weight gain, uric acid level, and renal function. The longer follow-up in some cases allowed a further more accurate reclassification. The category unclassified was avoided and was usually applied to the hospital records before adequate follow-up was available. The retinal findings were not used as a criterion for toxemia classification.

TABLE III. TOXEMIAS OF PREGNANCY

A. Peculiar to Pregnancy.—
- I. Vomiting
- II. Pre-eclampsia—mild
  —severe
- III. Eclampsia

B. Not Peculiar to Pregnancy.—
- I. Hypertensive disease—mild
  —severe
- II. Renal disease

Only objective signs and laboratory evidence were used to determine the variety of toxemia. Hypertensive disease present before pregnancy may be recognized prior to the twenty-fourth week while pre-eclampsia does not appear until after that period. The blood pressure in pre-eclampsia usually returned to normal limits within 3 to 4 months after pregnancy. In hypertensive disease the blood pressure elevation was usually present before and and commonly persisted indefinitely after the pregnancy. In mild pre-eclampsia the blood pressure ranged from 140/90 to 160/100. Elevation above these levels usually classified the toxemia as severe pre-eclampsia. Excessive weight gain and the onset and amount of albuminuria were also important in

the classification. The diagnosis of nephritis was determined from a past history of renal disease, persistent albuminuria before or after gravidity, many urinary formed elements, and reduced renal function. A high uric acid in the neighborhood of 6 mg. per cent usually placed the case in the severe pre-eclamptic group in the absence of azotemia. At times the differentiation of the variety of toxemia was difficult. Usually the case could be placed in a single category when all the objective factors and the follow-up were considered.

Because of some inadequacies in the records it was not possible to include all patients with toxemia in the present study. Only such cases as had complete clinical and laboratory examinations in addition to carefully recorded ophthalmoscopy and follow-up observations were evaluated. Records of 1,040 patients fulfilled these requirements and they were classified as follows:

Vomiting of pregnancy	92
Mild pre-eclampsia	367
Severe pre-eclampsia	205
Eclampsia	35
*Mild hypertension	172
*Severe hypertension	142
*Renal disease	27

Vomiting of Pregnancy

There were 92 cases of hyperemesis gravidarum with adequate ophthalmoscopic examinations at the New York Lying-In Hospital from 1934 to 1949. In most of this group the vomiting occurred during the first and second trimesters; in a small number it continued to term. In only two instances were retinal hemorrhages observed. In this series there were 12 spontaneous and therapeutic abortions, and 80 deliveries with four fetal deaths. Two of these infant deaths were attributed to obstetrical complications (placental separation and intrauterine infection). The third was that of a 2,900-gram infant who died on the third neonatal day following induction of labor for intractable vomiting. The fourth fetal death was of unknown cause. The mother had vomiting for several weeks in the fourth month of pregnancy and a superficial hemorrhage of the retina which subsequently disappeared. No therapeutic abortions for vomiting of pregnancy associated with retinal hemorrhage were considered necessary during the 16-year period at this clinic. The two cases with associated retinal hemorrhages will be presented in some detail.

R. M. (No. 254253), a 28-year-old para i, gravida ii, was admitted in the fifteenth week of pregnancy because of severe persistent vomiting. There was a 15-pound weight loss with dehydration and acetonuria. Retinal examination revealed a small fresh hemorrhage to the temporal side of the left optic disc. After 2 weeks' hospitalization for treatment the vomiting ceased and the patient was discharged. At the thirty-sixth week fetal movements suddenly and unexpectedly ceased; 2 weeks later a macerated 2,500-gram infant was delivered spontaneously. At this time re-examination of the optic fundi revealed normal vessels without hemorrhage; there was no evidence of toxemia. Autopsy permission was not obtained. Although the final cause of intrauterine fetal death is unknown, the hyperemesis gravidarum with the transient retinal hemorrhage appeared unrelated to the final outcome of the pregnancy.

D. K. (No. 404722), a 30-year-old para i, gravida ii, noted mild vomiting beginning in the sixth week of gestation. Examination of the retinal fundi at the eighteenth week revealed a single fresh superficial hemorrhage adjacent to the right disc with normal retinal

*Presented in "Part II, Retinal Changes in the Toxemias of Pregnancy." (To be published later.)

vessels. After several days the hemorrhage in the right eye faded and the vomiting rapidly subsided following supportive therapy. The subsequent course of the pregnancy was uneventful and a living normal infant was delivered at term.

The previously described extensive retinal hemorrhages associated with vomiting in pregnancy have not been observed in this study. If large areas of retinal hemorrhage are found, interruption is probably necessary as previously reported. On the other hand, small superficial retinal hemorrhages require careful frequent observation. If there is no progression in the abnormal retinal findings interruption of the pregnancy on the basis of these changes is not indicated.

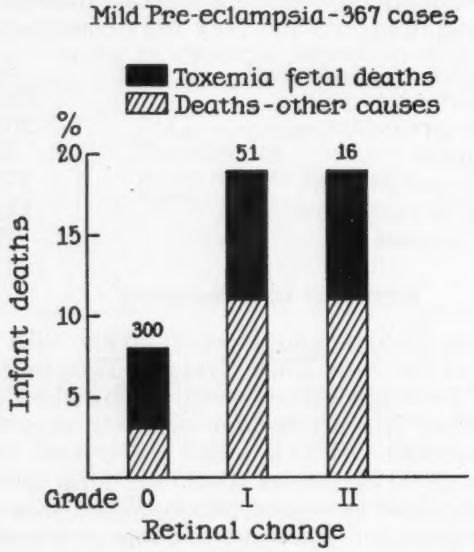

Fig. 1.

Mild Pre-eclampsia

Three hundred sixty-seven cases of mild pre-eclampsia were reviewed to determine the value of ophthalmoscopy in predicting the possible outcome. As was anticipated, the edema, albuminuria, uric acid level, blood pressure, and retinal arteriolar findings were all mild in degree. The blood pressure paralleled the retinal findings more closely than any other of the common abnormalities. There were 300 cases with no demonstrable retinal change (Grade 0) in mild pre-eclampsia (Fig. 1) with 24 fetal deaths, nine of which could be associated with other causes. Six of these infants had congenital defects and in the other three cases maternal diabetes appeared to be the cause of death. In this large group there were 15 deaths (5 per cent) without vascular retinal abnormalities, which might be attributed to the mild pre-eclamptic toxemia. Under Grade I, in a group of 51 patients, 3 (6 per cent) infant deaths were associated with the toxemia and an additional 3 (6 per cent) occurred in patients with maternal diabetes. In the Grade II category there was only one fetal death in a group of 16, or a 6 per cent fetal mortality. There were also two associated with maternal diabetes. The fetal death rate in this mild form of toxemia was accordingly essentially the same irrespective of the retinal findings. In the Grade II category with living infants the average duration of the toxemia was three weeks and the average time of onset was the thirty-sixth week. The vast majority of patients delivered spontaneously. One-half

of them had developed previous toxemia and one-fourth had at least three pregnancies. Some cases that were designated pre-eclampsia might be classified eventually as early hypertensive disease when additional follow-up observations are complete.

Severe Pre-eclampsia

Two hundred five cases of severe pre-eclampsia were studied. Edema, uric acid level, albumin, blood pressure, and retinal changes were all evaluated in each individual case. Blood pressure elevation and degree of retinal arteriolar change paralleled each other and in many instances appeared to indicate the cases in which fetal death might be expected. The other findings did not correspond to the same extent.

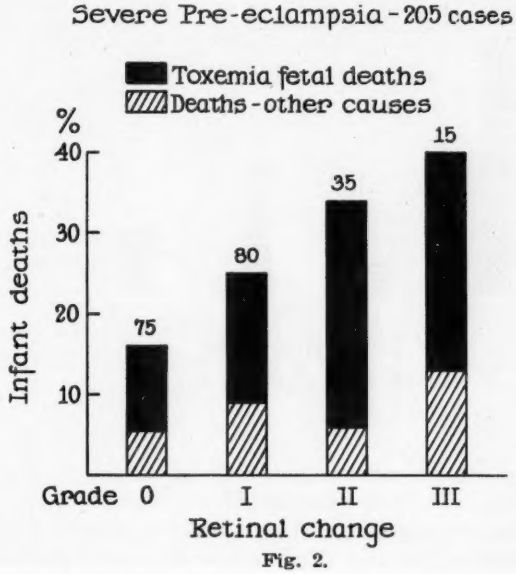

Fig. 2.

Among the severe pre-eclampsia group with Grade 0 retinal findings there were 75 cases with 12 fetal deaths. Four of these infants died of other causes than toxemia. Thus in this group there were eight fetal deaths (11 per cent) associated directly with the severe pre-eclampsia (Fig. 2). Among the severe pre-eclampsia group with Grade I retinal change there were 12 fetal deaths (15 per cent) in a total of 80 cases directly attributed to the toxemia. In the Grade II and Grade III classification there were 50 patients with 14 fetal deaths (28 per cent). Thus 41 per cent of fetal deaths in severe pre-eclampsia were associated with moderate or severe retinal vascular change. If the minimal retinal findings of Grade I are included, 80 per cent of all fetal deaths were associated with some vascular retinal alteration.

TABLE IV. SEVERE PRE-ECLAMPSIA, RETINAL GRADE II-III

	GRADE			
	II L*	II D*	III L	III D
Average week onset	32	29	33	30
Duration toxemia, days	22	24	17	25
Immature	0	7	1	2
Premature	15	4	4	4
Full term	8	1	4	0

*L = living; D = dead infant.

In the group with Grade II retinal changes and living infants the pregnancy was terminated prematurely in 70 per cent. The remainder, with two exceptions, delivered spontaneously in an average of 22 days from the onset of toxemia (Fig. 3). In this entire group the average week of onset of the toxemia was the thirty-second week (Table IV) and the total duration of the condition, measured from the initial blood-pressure elevation, was 22 days. There were approximately twice as many premature as full-term infants.

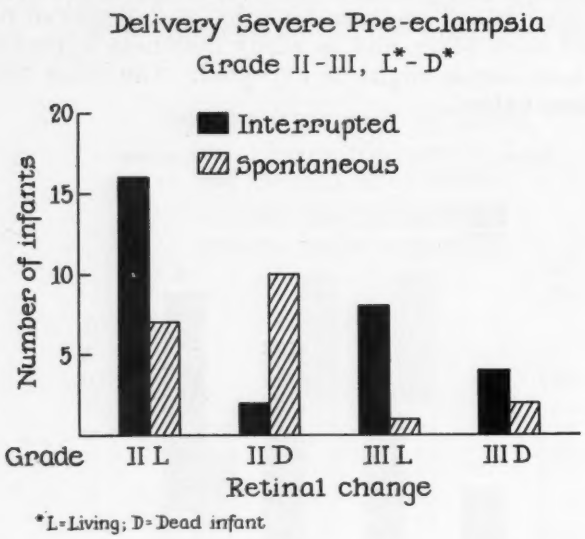

Fig. 3.

In the Grade II category associated with fetal death, delivery was spontaneous and interruption was not considered because of the marked prematurity of the infants. The average weight was 1,300 grams. Two were delivered by section; one was born alive and died in the neonatal period of a congenital anomaly. The other was associated with maternal diabetes; the infant was dead 24 hours prior to delivery. Although the clinical indication for interruption was present, the weight of the infants was such that the procedure was deferred. The average onset of the toxemia was the twenty-ninth week. The duration of the toxemia, measured from the initial blood-pressure elevation to the death of the fetus, was 24 days. The only term infant was associated with maternal diabetes. Sixty per cent of these infants were below 1,500 grams.

In the Grade III retinal group the patients with living infants were all considered for more immediate interruption as soon as the ophthalmologist found hemorrhage or transudate. The only spontaneous delivery in the group occurred during consideration of abdominal delivery. The average week of onset was the thirty-third and the average duration of the toxemia was 17 days. Among the Grade III with dead infants the weight of the infants again reduced the chances of survival with immediate interruption. The average weight was 1,900 grams; the time of onset was the thirtieth week of gestation and the total duration of the toxemia was 25 days. Two of the premature infants died because of associated congenital defects. Although the Grade III group comprised only 15 cases, the retinal findings were given serious consideration and 60 per cent of the pregnancies resulted in living infants. Brief summaries of two cases of severe pre-eclampsia with Grade II are presented.

R. A. (No. 496225), a 24-year-old white primigravida was admitted in June of 1948 during the thirty-seventh week of pregnancy because of elevated blood pressure, 160/120,

marked edema and excessive weight gain (14.2 kilograms) without albuminuria. Eye grounds showed severe localized and generalized spasm of retinal arterioles with considerable peripheral attenuation of arterioles. Uric acid rose to 5.0 mg. per cent and albuminuria 2 plus became manifest. On a medical regimen the patient improved clinically and the blood pressure fell to 130/90. In the fortieth week of pregnancy because of persistent and increasing retinal spasm induction of labor was decided upon and was successful. A midforceps delivery resulted in the birth of a 3,560-gram living infant. Postpartum renal function tests were normal. Seven months following delivery blood pressure was 120/80 and there was no albuminuria. Fig. 4 shows the local and general spasm of Grade II seen in this patient.

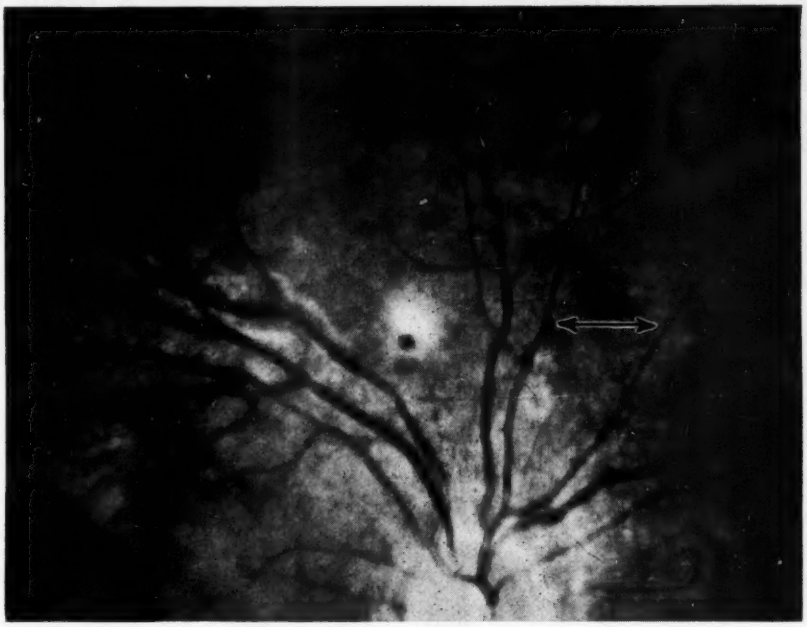

Fig. 4.—R. A. showed local spasm (arrows). There was moderate generalized spasm farther in the periphery.

J. P. (No. 495299), a 40-year-old white primigravida, was admitted in May of 1948 in the thirty-fourth week of pregnancy because of a blood pressure of 190/120, 3 plus albuminuria, uric acid of 4.1 mg. per cent, and a 2 plus edema. Retinal examination revealed a few areas of moderate local spasm; there was considerable peripheral spasm which was classified as Grade II. Principally because of the severe nature of the pre-eclampsia and the retinal change cesarean section was performed and a 1,690-gram infant delivered who was subsequently discharged as well. The retinal vessel spasm subsided during the first week post partum. Fifteen months after delivery the blood pressure was 120/80 and the urine was free of albumin, indicating the complete reversibility of the phenomena.

Eclampsia

Thirty-five patients with eclampsia had retinal examinations either before or after the development of convulsions. At times difficulty was experienced in obtaining accurate observations from very ill patients because they could not cooperate. A number were not satisfactorily examined until several days after the convulsions so that a part of the retinal changes may have subsided by that time. In 17 eclamptic patients who had a relatively mild form of the disease the examination failed positively to identify significant alterations; there were no fetal deaths in this group (Fig. 5). Seven of these had blood

pressure elevations of 180/110 or more. This was, however, not sustained and was recorded only on the day of convulsions. Eight were classified in the Grade I retinal category with two fetal deaths (25 per cent). One was associated with severe pre-eclampsia and postpartum eclampsia, while the other fetal death followed a sudden unexpected convulsive episode after a single day of elevated blood pressure. In the Grade II group of six, there were three fetal deaths (50 per cent), one of which was probably caused by erythroblastosis. A second patient developed convulsions at about the twenty-fifth week of gestation which ended in an induced abortion, the fetus weighing 430 grams. The third developed convulsions early in the third trimester and delivered a 1,900 gram macerated deadborn infant. Among the four in Grade III with hemorrhage and/or exudates, one immature fetal death was preceded by bilateral inferior retinal detachments. This process subsided and disappeared following the termination of the pregnancy by induction. Twelve years later the visual fields were normal with 20/20 vision in both eyes. The infants in the other 3 cases were born alive and discharged well.

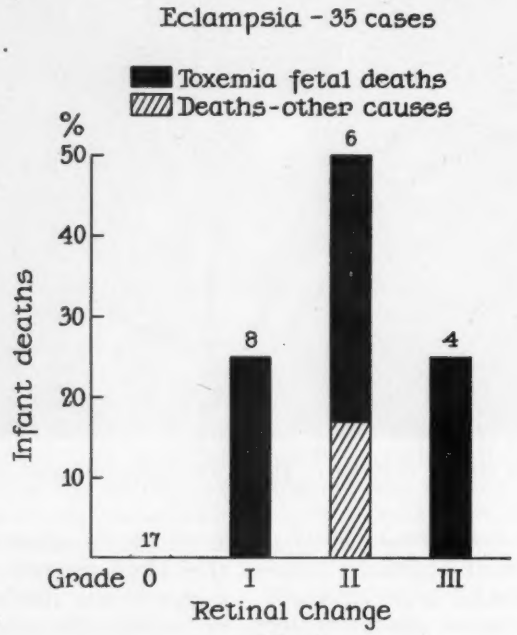

Fig. 5.

Comment

At the New York Lying-In Hospital during a period of 16 years (1933-1949) approximately 58,000 deliveries occurred. No maternal death resulted from hyperemesis gravidarum. In addition no therapeutic abortions were performed for intractable vomiting of pregnancy in patients with retinal abnormalities. Two patients showed small retinal hemorrhages which disappeared and the pregnancies went to term. The type case reported in the literature with large areas of flame-shaped retinal hemorrhage associated with a rapid downhill course has not been observed on our service. A 3.6 per cent maternal mortality associated with hyperemesis gravidarum was reported in 1941 by Ballantyne[29] from Scotland, and six deaths from 1906-1936 were reported by Schjott-Rivers[27] from Oslo. Our experience, as previously described, is quite different.

The higher standard of living, improved nutrition, and the early hospitalization in cases of intractable persistent vomiting have probably played some part in reducing the severity of the disease. Some of the cases of severe vomiting in the past have been attributed to encephalitis and associated with retinal hemorrhage, paralysis of extremities, and sudden death. The finding of advanced renal disease by Tillman[25] in two fatal cases suggested that an early urinary-tract investigation may be of practical importance. Ballantyne[29] believed that the initial eye findings were a retrobulbar optic neuritis with a central visual field defect and scotomas which was followed by edema of the disc and hemorrhages. This was suspected in one case described by Schjott-Rivers[27] but microscopic sections revealed no abnormality. No such entity has been found in our patients at the Lying-In Hospital during the past 16 years. The presence of advanced renal disease, encephalitis, hepatitis, or thrombocytopenia are some of the entities in addition to the pregnancy per se which may be responsible for the retinal findings and the vomiting.

Although Stander,[24] Tillman,[25] Schjott-Rivers,[27] and Ballantyne[29] advocated the immediate interruption when retinal hemorrhages are recognized, the findings in our two cases would suggest the adoption of a more conservative regimen. If a small superficial hemorrhage is present, observation for several days will indicate whether there is improvement, as occurred in our cases, or further advancement of the disease. If large hemorrhages are seen, as previously reported, interruption is probably indicated.

From the data collected in 367 cases of mild pre-eclampsia the retinal examination is of definite value. It is true that the percentage of fetal deaths was essentially the same in Grade 0, I, and II retinal changes. However, by following the arterioles in the milder cases, a base line for the interpretation of more advanced changes of possible severe pre-eclampsia will be available. This will greatly increase the value of such subsequent examinations. In addition spasm oftentimes indicated the necessity for the premature termination of the pregnancy with a resultant living infant. The more advanced arteriolar findings in Grade II were in some instances possibly related to previous vascular damage associated with repeated pregnancies and recurrent toxemias. The Grade II findings did not indicate any greater severity in the toxemia from a clinical point of view as almost all began late in pregnancy and the pregnancy terminated spontaneously. There are, in our opinion, vascular changes frequently present in mild pre-eclampsia but they cannot be recognized by the methods of investigation currently employed. The only other finding of interest in this mild pre-eclamptic group was the high percentage of infant deaths associated with maternal diabetes in all retinal grades.

In severe pre-eclampsia a review of 205 cases indicated that the advancement of retinal arteriolar changes was directly correlated with fetal death. In spite of recent attempts[32] to secure further living infants by premature interruption of pregnancy the fetal mortality among the Grade II was 34 per cent as compared to 16 per cent in Grade 0. It becomes evident then that there were twice as many fetal deaths when the patient had Grade II retinal changes as compared to the patients in Grade 0. Fetal death also may occur when no spasm is evident. However, if spasm develops, the possibility of fetal death is increased and in general the premature termination of pregnancy should be seriously considered. The total clinical picture is of more importance than any individual sign and this includes the retinal examination. Our experience indicated that fetal death was likely to occur within 3 weeks after the onset of arteriolar spasm (Grade II) in severe pre-eclampsia. The onset of this period is judged by the time of the initial diagnosis of the toxemia. The presence of increasing vascular spasm on subsequent retinal examinations

is undoubtedly a very ominous sign. However, if the retinal vascular picture remains the same or is reduced, this alone is no real indication of improvement and termination should be seriously considered prior to the third week of the toxemia.

If hemorrhages or transudates are observed in the retina in the course of a severe pre-eclampsia (Grade III) interruption should be performed at the earliest possible time. If the fetus is not viable and the pregnancy is allowed to proceed the fetus will usually die during the first two or three weeks after the recognition of the condition. The all important factor is the time of onset of the pre-eclamptic toxemia, which very definitely limits the number of living infants. This is well illustrated in Table IV. In both Grades II and III there is a difference in the average duration of the gravidity of three weeks between those that terminate with a living or dead infant; the latter are associated with the earlier onset of toxemia and a larger group of immature infants (500-1499 grams). Repeated ophthalmoscopy has indicated that almost all of the abnormal retinal findings return to normal within three months in the pre-eclamptic group. The absence of the "copper wire" arterioles and the absence of thickened arteriolar walls help in many cases to exclude the diagnosis of hypertension.

In the eclamptic group, one-half of the patients failed to develop retinal vascular aberrations. The eclamptic mothers without retinal changes all delivered living infants. As the severity of the retinal vascular changes increases, the number of patients with eclampsia early in the third trimester also increases, with associated premature and immature deliveries with few surviving infants. Patients with eclampsia and Grade 0 findings, in contrast, usually develop convulsions late in the third trimester and are subsequently delivered of an average-sized living fetus. Those with the more advanced retinal grades almost always have, in addition to eclampsia, a previous hypertensive or renal disease.

Conclusions

1. Ophthalmoscopy is an essential examination in all cases of hyperemesis gravidarum, severe pre-eclampsia, and eclampsia.

2. In vomiting of pregnancy superficial transient retinal hemorrhages do not require interruption of the pregnancy; large retinal hemorrhages probably constitute a sufficient reason for interruption.

3. Other causes for retinal hemorrhage with vomiting of pregnancy, such as advanced renal or hypertensive disease, hepatitis, encephalitis, and thrombopenia, should be considered.

4. Our experience indicates an absence of large retinal hemorrhages and maternal deaths at the New York Lying-In Hospital from hyperemesis gravidarum in the past 16 years.

5. The slight retinal changes observed in mild pre-eclampsia are of prognostic significance and the findings may be of very considerable value as a base line in the interpretation of subsequent developments.

6. In no instance were Grade III or IV changes noted in the 367 patients with mild pre-eclampsia.

7. The development of spasm or increase in its severity may frequently constitute an indication to terminate the pregnancy for the welfare of the mother and baby.

8. In severe pre-eclampsia retinal vascular changes help to clarify the diagnosis and the severity of the toxemia.

9. In severe pre-eclampsia Grade II retinal change suggests strongly that the pregnancy should be terminated. Procrastination to permit further development of the fetus may at times be justified. Experience indicates that this period should not exceed three weeks. In Grade III termination should be performed at the earliest possible time irrespective of the estimated weight of the fetus.

10. The recent improved infant survival rate in severe pre-eclampsia with marked retinal vascular change is related to early interruption. Most infant deaths occur in the group in which the onset of toxemia is prior to the period of viability.

11. In eclampsia the finding of normal fundi indicates an excellent prognosis for both the mother and the infant.

12. The more advanced retinal Grades II and III in eclampsia usually indicate previous renal and hypertensive toxemia, early onset of the disease, and high fetal mortality.

13. Retinal examination reveals important objective information concerning the toxemias peculiar to pregnancy, furthers their accurate diagnosis, and refines their management.

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LESIONS OF THE VAGINAL VAULT FOLLOWING COMPLETE HYSTERECTOMY*

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THE development of proliferative lesions or other complications in the vaginal vault following complete hysterectomy is relatively uncommon. Two exceptions to this are granulation tissue and various fistulas. With these exceptions, a review of the literature revealed few descriptions of other such lesions.

As early as 1880 case reports were published with descriptions of nodules of tissue that develop in the scar line of the vagina following complete hysterectomy for malignant uterine disease. Cullen described several of his own cases in which vaginal hysterectomy was performed for adenocarcinoma of the body of the uterus and in which there were recurrences at the site of the vaginal scar. Geist stated "that the operative scar may be the site of ovarian metastases following both vaginal and abdominal operations."

Nodules of endometrial tissue in the episiotomy scar have been reported but very few nodules of such tissue have been noted in the vaginal scar following complete hysterectomy. Even less often described is prolapse of a portion of the oviduct or a portion of the bowel.

Fistulas of the various types, more commonly vesicovaginal or ureterovaginal, are observed in all clinics where hysterectomy is performed. This complication has been adequately discussed in numerous other reports and therefore will not be considered here.

Material

The material in this report has been obtained from eight patients in whom lesions were present in the vaginal vault scar line following complete hysterectomy. Six of these patients were treated at the St. Luke's Hospital. The tissues from these patients were examined by Dr. Edwin F. Hirsch of the Department of Pathology of the St. Luke's Hospital. The history and tissues from two of the patients were kindly furnished by Dr. John I. Brewer of the Passavant Memorial Hospital, Chicago, and the pathologic report was supplied by Dr. Mark Wheelock of the same hospital. The cases are listed in Table I.

TABLE I

Endometriosis	1
Prolapse of the oviduct	1
Carcinoma of the cervix	2
Carcinoma of the endometrium	2
Sarcoma of the uterus	1
Kruckenberg tumor of the ovary	1

*Presented at a meeting of the Chicago Gynecological Society, March 16, 1951.

CASE 1.—A 54-year-old private patient of Dr. John I. Brewer was operated upon vaginally in 1945 because of symptomatic uterine fibromyomas. Approximately five years after this operation the patient was seen because of vaginal spotting of blood. There was a grape-size, friable, vascular tumor at the apex of the vaginal vault. The tissue was excised and examined microscopically.

Diagnosis.—Endometriosis of the vagina.

CASE 2.—A 28-year-old woman was operated upon vaginally in 1950 for symptomatic uterine fibromyomas. Two months after operation there was a soft, red, nontender polypoid growth (15 by 10 by 5 mm.) in the scar line of the vaginal vault. The microscopic examination revealed stroma tissue with marked chronic exudative inflammation, arranged in blunt folds with deep crevices like uterine tube. The blunt folds were lined by rather large columnar or cuboidal epithelium. A second biopsy three weeks later revealed typical uterine tube tissue with less inflammatory reaction. The tissue in the vault was treated with electrocautery.

Diagnosis.—Uterine tube tissue with chronic exudative salpingitis.

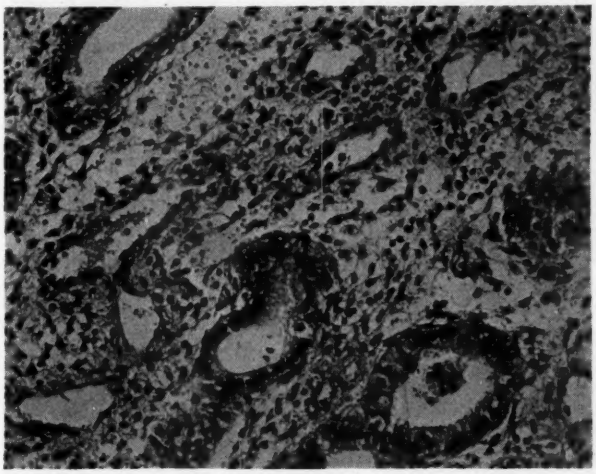

Fig. 1 (Case 1).—(No. 22296) Endometriosis in the vaginal vault. (×198.)

CASE 3.—A 56-year-old patient was operated upon abdominally in 1940 because of uterine bleeding twelve years after the menopause. Microscopic examination of the cervix revealed squamous-cell carcinoma which had been unrecognized clinically. Three years later the patient reported vaginal spotting of blood. There were several small, roughened polyps in the vault scar. A biopsy of this tissue revealed recurrent squamous-cell carcinoma. Prior to the recurrence this patient had received some deep pelvic x-ray therapy at the St. Luke's Hospital followed by an undetermined amount at another institution. A follow-up after the recurrence was not possible as the patient left this city.

Diagnosis.—Squamous-cell carcinoma recurrent from the cervix in the vagina.

CASE 4.—A 46-year-old private patient of Dr. John I. Brewer was operated upon in 1948. A complete abdominal hysterectomy was performed. Microscopic examination of the cervix tissues revealed a squamous-cell carcinoma which had been unrecognized clinically. Eight months later there was a tumor mass in the lower abdomen which proved to be a large (20 cm.) left ovarian tumor. This tumor mass was in part a cystadenoma and, in part, a metastatic squamous-cell carcinoma. Postoperatively the patient was given 8,000 r of deep pelvic x-ray. Six months after this second operation there was a red polyp 2 cm. in diameter in the vaginal scar. A biopsy of this polyp revealed metastatic squamous-cell carcinoma of the

vaginal vault. Radium needles were placed in this polyp for a total of 2,000 mg. hr. At the present time this patient is well and apparently free of cancer.

Diagnosis.—Metastatic squamous-cell carcinoma of the vaginal vault.

CASE 5.—A 56-year-old woman was operated upon abdominally in 1948 because of vaginal bleeding seven years postmenopausally. A complete abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The significant finding at operation was an ulcerated area 2.5 cm. in diameter in the endometrium of the fundus on the anterior wall. Microscopically the myometrium in this region was extensively ingrown by many large and small

Fig. 2.

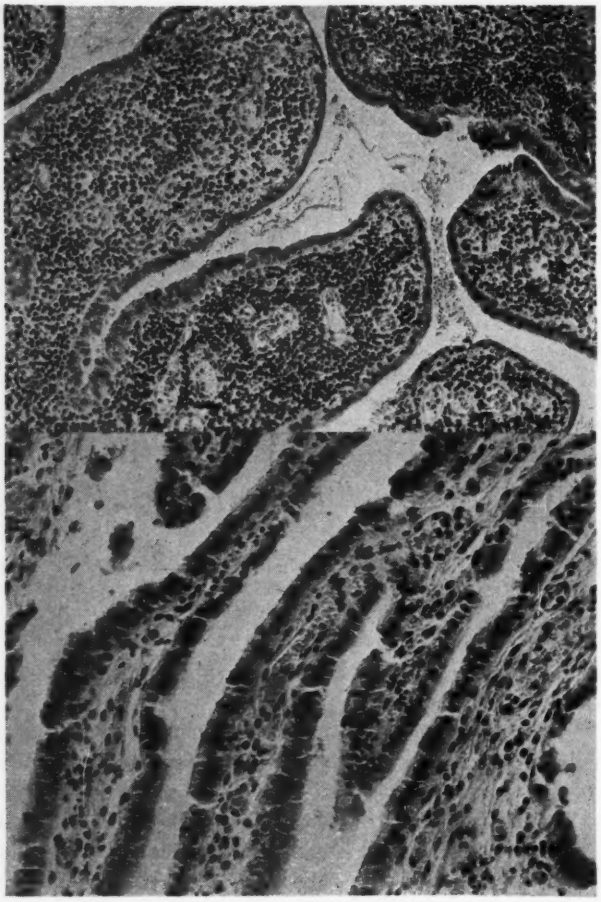

Fig. 3.

Fig. 2 (Case 2).—(No. 6450-50) Uterine tube tissue in the vaginal vault. There is a chronic exudative salpingitis. (×142.)

Fig. 3 (Case 2).—(No. 6842-50) Uterine tube tissue three weeks later showing less inflammatory reaction. (×198.)

irregular masses of atypical epithelial cells, arranged in mosaics, not in tubules. The diagnosis was squamous-cell carcinoma of the body of the uterus. This patient received postoperative x-ray therapy but she refused to complete the treatment. Eighteen months after operation there was a region in the vaginal scar that had the appearance of an ulcer or granulation tissue. Microscopically the tissue was similar to the original tumor.

Diagnosis.—Recurrent squamous-cell carcinoma of the endometrium in the vagina.

CASE 6.—A 34-year-old woman was operated upon abdominally in 1938 because of a large abdominal mass which proved to be a pseudomucinous cyst of the left ovary and a generous-size uterus. A subtotal hysterectomy and bilateral salpingo-oophorectomy were performed. The microscopic diagnosis was glandular carcinoma of the body of the uterus and multilocular pseudomucinous cyst of the left ovary. The patient received a full course of deep pelvic x-ray. She was well until nine years later at which time she was seen because of vaginal spotting of blood. The cervix could not be visualized because of an adhesive vaginitis. There was a fixed orange-size mass in the midline of the lower abdomen. The cervix was dilated and a large amount of clear brown fluid was released. One month later the abdominal mass including the cervix was removed and it contained carcinoma similar to the original tumor.

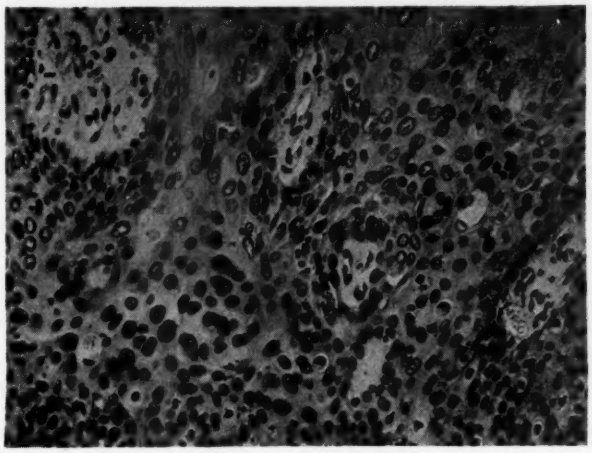

Fig. 4 (Case 3).—(No. 1347-43) Squamous-cell carcinoma recurrent in the vagina from an early clinically unrecognized squamous-cell carcinoma of the cervix. (×198.)

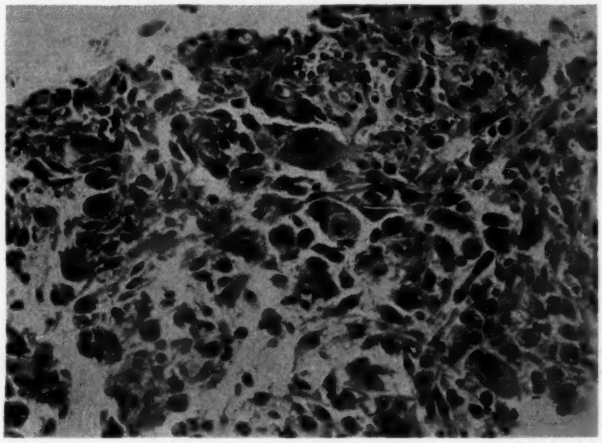

Fig. 5 (Case 5).—(No. 5956-49) Anaplastic squamous-cell carcinoma recurrent in the vagina from squamous-cell carcinoma of the body of the uterus. (×198.)

On March 15, 1948 (nine months later), there was a small region in the scar that appeared to be granulation tissue. A biopsy of this proved to be carcinoma of the vaginal vault (metastatic). The patient was given a course of intravaginal x-ray therapy. Again on Nov. 15, 1948, another biopsy of another ulcerated region revealed a similar recurrent carcinoma of the vaginal vault. Another course of intravaginal x-ray therapy was given. There has been no further recurrence to this date.

Diagnosis.—Glandular carcinoma of the endometrium recurrent in the vagina.

CASE 7.—A 43-year-old woman was operated upon vaginally in 1946 because of symptomatic uterine fibromyomas. Morcellation was necessary because of the size of the tumors. The microscopic report was sarcoma of the uterus. This patient was seen every six months postoperatively. Four and one-half years after operation there were two red polyps on a broad base arising from the scar. One was 10 and the other was 7 mm. in diameter. This tissue was removed widely and contained tumor tissue similar to the sarcoma in the uterus.

Diagnosis.—Recurrent sarcoma of the uterus in the vagina.

Fig. 6 (Case 7).—(No. 5121-50) Sarcomatous tissue in the vagina recurrent from sarcoma of the uterus. (×198.)

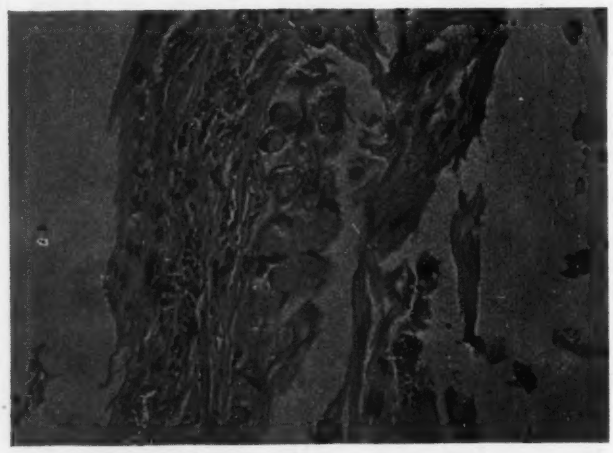

Fig. 7 (Case 8).—(No. 4437-49) Signet-ring cells from vaginal recurrence identical to those seen in the Krukenberg tumor in the ovaries (primary in the bowel). (×270.)

CASE 8.—A 53-year-old woman was operated upon abdominally in 1946 because of an abdominal tumor which proved to be a large mucoid carcinoma of the bowel with metastases to the mesenteric lymph nodes. The patient was readmitted in 1948 because of another abdominal mass. At operation this proved to be a bilateral so-called Krukenberg tumor of the ovaries.

Two years after this second operation there was a smooth, red, 3 to 4 mm. nodule in the scar line of the vagina. Microscopic examination of this nodule revealed signet-ring

cells similar to the cells in the ovarian tumors. This patient had further recurrence in the vagina and in the rectum. She died within the last month as a result of this tumor.

Diagnosis.—Metastatic carcinoma (primary in the bowel) in the vagina.

This discussion will begin with the more common and, in general, the more benign lesions that develop in the vaginal vault after complete hysterectomy.

Benign Lesions in the Vaginal Scar

Granulation Tissue.—This may be a source of symptoms in the patient. There is frequently a vaginal discharge which at times may be accompanied by blood. Grossly the lesion is most often in the form of a small, 3 to 5 mm., red, polyp-like nodule or nodules in the scar in the vagina. Granulation tissue may also have the appearance of a small ulcer. The occurrence of carcinoma metastases or extension after hysterectomy may simulate either of the above forms of granulation tissue. The proper recognition and differentiation between granulation tissue and possible malignant tissue is most important in patients who have been operated upon for malignant disease of the female pelvis. A biopsy of apparent granulation tissue in such patients is therefore necessary before treatment is instituted.

Specific granulation tissue must be considered in the differential diagnosis. A case treated by Dr. Ronald R. Greene illustrates this.

A 32-year-old woman was first seen in 1948 because of right lower quadrant pain and a bloody vaginal discharge. There was a tender, cystic, right adnexal mass, 8 cm. in diameter. There was also a mass in the vaginal vault scar 1 by 3 cm. that resembled the fimbriated end of the uterine tube. The patient had had an abdominal operation in 1944 and a complete abdominal hysterectomy in 1947. Information regarding these operations is not available.

A clinical diagnosis of right ovarian tumor and prolapsed uterine tube was made. The patient was operated upon abdominally and a right ovarian serous cystoma was removed with difficulty because of dense adhesions. The uterine tube or tubal remnant could not be identified. The vagina was opened and the vaginal mass with the attached mucosa was excised. The microscopic diagnosis was condyloma acuminatum. The sections were not available for this report.

Benign Papilloma.—This is apparently a rare lesion. In Lewis' *Surgery,* Wynne mentions the occurrence of a benign papilloma in a patient who had a hysterectomy performed for adenocarcinoma of the uterus.

A case has been described by Ferguson and Young in which two soft bleeding projections were removed from the scar in the vagina one month after vaginal hysterectomy for carcinoma of the cervix. Microscopically, the tissue was similar to a villous papilloma. The authors felt that this was not of tubal origin but rather that they were dealing with a papilloma derived from local overgrowth of mucosa which had assumed a papillomatous state. The microscopic findings here are not unlike those we observed in the first biopsy tissue we obtained in the case of the prolapsed oviduct, but which on subsequent biopsy revealed uterine tube tissues in a normal pattern.

Endometriosis.—Goodall states that both primary and secondary endometriosis is fairly common. The secondary form "is due to an endometrial lesion in the pouch of Douglas or in the recto-vaginal septum and that it burrows through the vaginal sheath." There is no mention in his text of its occurrence after hysterectomy. In a review of the literature by Tornqvist seven cases of endometriosis of the vaginal vault following operation for prolapse of the uterus were reported. Similar symptoms developed in six of the seven cases, which consisted of a sense of distention, burning, or pain in the

scar, increasing in degree at what would have been the menstrual time. Reich and associates reported a case of endometriosis of the vagina following vaginal hysterectomy. This patient noted a return of what appeared to be cyclic bleeding. The lesion was flat, bluish, 4 to 6 mm. in diameter immediately below the scar on the left posterior wall. The biopsy revealed endometriosis of the vagina. The original findings were reviewed and there was no evidence of endometriosis or adenomyosis in the cervix or the uterus.

Prolapse of the Oviduct.—Prolapse of a portion of the oviduct through the vaginal vault incision postoperatively is relatively uncommon. This is not a serious complication and when the diagnosis is made the treatment is simple, namely, cauterization or excision. In addition to the case described in this report we have seen it on one other occasion several years ago. Heaney found two instances of prolapsed oviduct shortly after he had reported his series of 565 vaginal hysterectomies in 1934. McElin and Ferris of the Mayo Clinic reported two of their own cases and cited six other instances in the literature, all of which followed vaginal hysterectomy.

Prolapse of a Portion of the Bowel.—This rare lesion is a serious complication. Reports in the literature are few. In 1949, Dr. Paul Fox described a case of prolapse of a portion of the ileum through an opening in the scar of the vagina. This occurred fifteen months after vaginal hysterectomy and repair for complete procidentia in a 74-year-old woman. In this instance it was necessary to enlarge the opening to replace the intestine. The opening was then closed with a purse-string suture. This was well healed at a three months checkup. One other case mentioned by Fox was reported by Rieunau in 1933. Fourteen years after vaginal hysterectomy a loop of small bowel prolapsed through the vaginal scar. This was repaired through an abdominal incision.

Kennedy states that he had two cases in which a portion of the omentum had prolapsed into the vagina but he has never experienced a case in which bowel had prolapsed.

More numerous reports of prolapse of the bowel through the vaginal wound were found at the turn of the century and were listed by Cullen in his discussion of the causes of death following vaginal hysterectomy. Eight were mentioned. In all of these cases some portion of the bowel had become adherent to the vaginal vault wound and in several fecal fistulas had developed.

An explanation is lacking for the fact that prolapse of the intestine or oviduct through an opening in the vaginal scar is reported only after vaginal and not after abdominal hysterectomy.

Malignant Lesions in the Vaginal Scar

Carcinoma of the Body of the Uterus.—These small metastatic growths may be submucous or upon the mucous membrane where they suggest an implantation of carcinoma cells from the discharge of the uterine cavity. The submucous ones are due to lymphatic extension, though the path must be retrograde for some part of its course.

Metastasis to the scar in the vaginal vault is less common. Cullen reports most of the cases that are to be found. The metastatic nodules were observed following both vaginal and abdominal hysterectomy. Cullen lists a case of Schopf's in which a carcinoma nodule was noted in the scar and nowhere else in the body. In another case of Hofmeier's following vaginal hysterectomy a nodule as large as a walnut was found in the scar.

The appearance of the recurring lesion is not uniform. The lesion may simulate granulation tissue or it may be nodular as small as a lead shot or as large as a walnut as described above. It may also appear as an ulcer.

Carcinoma of the Cervix.—The incidence of spread of carcinoma of the cervix to the vagina is high. However, because of the accepted present-day nonsurgical treatment of this lesion one would seldom see this lesion in the postoperative vaginal scar. An early clinically unrecognized carcinoma of the cervix subjected to hysterectomy might be the source of this recurrence. Both cases reported here are examples of this.

In Cullen's era, both vaginal and abdominal hysterectomy were performed in the treatment of cervical carcinoma. Six cases were reported by Cullen.

Sarcoma of the Uterus.—Meigs states that leiomyosarcoma of the uterus or cervix may invade the vagina, recurring in the vaginal scar following complete hysterectomy. Laroyenne and Marion, according to Meigs, reported a sarcoma arising in the vaginal scar six years after vaginal hysterectomy for fibromyomas of the uterus. In our own case the interval was four years.

Chorionepithelioma of the Uterus.—The vaginal vault is one of the most common sites of metastases of chorionepithelioma. In fact, the diagnosis may first be suspected if not made on the basis of the metastatic nodule in the vagina. Specific instances of the recurrence of chorionepithelioma in the vaginal scar after hysterectomy were not found in the literature reviewed.

Ovarian Malignancies.—Geist states that "the operative scar may be the site of metastases following both abdominal and vaginal hysterectomy. The process may be due to implantation of viable tumor cells directly into the wound, to direct extension, or may represent a true metastasis arising by way of the lymphatics or vascular channels. Occasionally there may be a long latent period following removal of the original neoplasm before the appearance of the tumor within the operative scar." Specific cases of recurrence of malignant ovarian lesions in the operative scar were not found in our review of the literature.

Summary

Benign and recurrent malignant lesions occur in the vaginal scar line following complete hysterectomy. The incidence, with the exception of granulation tissue, is low.

Eight cases are reported, two with benign lesions and six with recurrent malignant lesions in the vaginal scar.

The appearance of granulation tissue varies; it may be an elevated red nodule, or it may be similar to an ulcer of the vaginal mucous membrane. In like manner malignant recurrence in the vaginal scar may assume one of the above forms. The importance of correct diagnosis is emphasized.

Prolapse of a portion of the oviduct or some portion of the bowel is observed only after vaginal hysterectomy and not after abdominal hysterectomy. Oviduct prolapse is not a serious complication and requires only the correct diagnosis to institute the simple treatment necessary. In contradistinction, prolapse of bowel through the vaginal wound is serious and requires more radical treatment.

Malignant lesions may recur in the vaginal scar by implantation of viable cells, by direct extension, or by lymphatic or vascular extension.

Biopsy is a necessary procedure in the differential diagnosis of these various lesions.

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Discussion

DR. HARRY BOYSEN.—In their initial statement the authors state that these lesions are "relatively uncommon," but they do not tell us how uncommon they are. I was interested, and had our results at the Presbyterian Hospital looked up. We found that we have performed 767 vaginal and 255 abdominal total hysterectomies in 1949 and 1950, inclusive. Of this group 20 were brought back to the hospital as outpatients for biopsy or cautery. In this group only one malignancy was found. This patient had been operated upon abdominally and a total hysterectomy had been done for uterine fibromyomas. This diagnosis had been substantiated by the sections microscopically. Later she developed a mass in the pelvis which was biopsied and a diagnosis of sarcoma made. In reviewing the previous sections and cutting more sections from the original blood it was apparent that the original tumor was a sarcoma.

There were no malignancies found among the other nineteen patients. This can be explained, I believe, by the fact that we operate upon very few (if any) known cervical carcinomas and all that are unrecognized preoperatively but discovered by the pathologist are given postoperative deep x-ray therapy. This is also true of endometrial carcinoma. There is very little more to be added to what Drs. Beebe and Edwards have stated regarding malignancies recurring in the vaginal vault. Suffice it to say that unless all the malignant cells are excised or adequately irradiated recurrences either by implantation or lymphatic extension may result.

Although only 20 patients were seen at the hospital I am certain that many more were cauterized in the offices. The exact percentage is hard to estimate but in my experience I would say that about 20 per cent will need either electric coagulation or chemical cautery of small areas of granulation tissue which bleeds, causes some pelvic tenderness or vaginal discharge. Of these I am sure a higher percentage are found following vaginal than abdominal hysterectomies.

In regard to prolapse of the oviduct, we almost never see it any more. As a complication following vaginal hysterectomy it is becoming almost as much of a rarity as the prolapse of a loop of small bowel or omentum. This probably can be explained by improvement of surgical technique, catgut, and postoperative care.

It is surprising to find only one case of endometriosis of the vault reported. At present I have two patients in their middle thirties on whom I did vaginal hysterectomies who had extensive endometriosis of the rectovaginal septum. In one of these I left one ovary and in the other, both ovaries. These patients have been relieved of all their symptoms except that at periodic intervals they will notice a brownish discharge for a day or so with an associated

pelvic discomfort of a minor degree. These patients have some thickening and induration of the vault but no typical blue dome cysts.

Case 7 certainly revives the old criticism of vaginal morcellation of pelvic tumors which is very difficult to justify when the tumors turn out to be malignant. Probably the less said the better as we are just as guilty as the essayists in this regard. It is not, however, the operation of choice and the possibility of a malignancy should be constantly borne in mind.

DR. BERNARD I. COOPERSMITH.—I would like to add one more case to this list. The patient was a 45-year-old woman who came in with a history of having had a vaginal hysterectomy performed about six months previously. She had persistent vaginal spotting from the time of the operation. Upon examination we found what appeared to be granulation tissue in the vault and proceed to cauterize it. She returned in a week and the granulation tissue was still present. A biopsy was performed and the pathologic report was chronic granulation tissue with marked leucocytic infiltration. Because she had had the persistent bleeding for over six months, a blood count was done. The white count was over 200,000. Subsequently a diagnosis of chronic myelogenous leucemia was made.

DR. EDWARDS.—As far as I know there is no paper in the literature that has collected and described all these lesions that occur in the vaginal vault after complete hysterectomy. There are many isolated case reports. This was the reason for getting this series together. Our experience is a little different from that of Dr. Boysen; we find that about 50 per cent of women after total hysterectomy have granulation tissue in the vault of the vagina. We find less after vaginal hysterectomy. I think that is due to the fact that they close their vaginal hysterectomies as they do; we close ours laterally and medially.

Another thing that has always been of interest to me—I have never seen but one carcinoma of the endometrium with metastases to the vaginal vault. I think that has been the experience of Dr. Gardner and Dr. Jones. There are a few cases reported in the East. As I understand, they show as high as 10 per cent recurrence in the vaginal vault. You can imagine the pathologist's state of mind when the clinician sends some tissue from the vagina knowing the woman had a carcinoma of the small bowel and then a Kruckenberg tumor removed and she has nodules in the vagina. We took some scrapings, placed them in Zenker's solution and sent them to the pathologist, and this is the report I received from Dr. Hirsch: "This is a very peculiar specimen. There are some signet-like cells. There are some mucus-like cells. I believe you should take another biopsy."

DR. BEEBE (Closing).—There is little to add to the report except that certainly if there is ever any question in our mind as to what the tissue may be, it is very simple to take a biopsy. It is true that where we are not worrying too much about carcinoma, we will not worry much about biopsy. But if there has been a malignancy, biopsy is the method of choice.

TRUE SACCULATION OF THE CONTRACTILE PORTION OF THE PREGNANT UTERUS*

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(From the Obstetrical and Gynecological Departments of the Michael Reese Hospital)

SINCE this material on true sacculation of the pregnant uterus was prepared for presentation nearly two years ago, O. W. Hess[1] published a very interesting article based on two rare cases of sacculation operated on by him.

A total of only six other cases may be gleaned from the literature. The purpose of this presentation is to discuss four additional verified cases and to establish the condition as an important pathological obstetrical entity.

Probably because of the rather meager evidence supplied by the previously reported cases, obstetrical textbooks almost ignore the subject, but, in the light of my experience, it occurs much more commonly than is generally supposed. Standard textbooks list more than a score of predisposing causes for spontaneous rupture of the uterus in pregnancy and labor; however, they omit sacculation, which I am convinced is a most important etiological factor in this, as well as in several other grave obstetrical complications.

It should be emphasized that true uterine sacculation differs widely from the functional malformations described by Rudolph.[2] The latter are characterized by asymmetrical uterine contraction and relaxation resulting in "ballooning out" of a portion of the uterus which disappears after escape of the amniotic fluid and is treated by "intelligent expectancy." True sacculation, on the other hand, is characterized by an ovoid structure, the wall of which measures from 1 to 2 mm., possessing a small aperture connecting it with the pregnant uterine corpus.

The first of my small series of cases is comparable to the one reported by Shaw[3] but has additional illuminating and instructive features. I saw the patient first in November, 1937. She was 41 years old, weighed 140 pounds, was 5 feet tall, and had mild generalized hirsutism but was losing the hair of her scalp. She menstruated scantily every ten months beginning at age 18 years. She married at age 26 and was later treated for sterility, and was told her uterus was infantile. She was widowed for seven years after seven years of marriage. She visited me three months after her second marriage in 1937 and three weeks after one of her infrequent, scant menstrual periods, complaining only of pressure in the abdomen, and still lamenting her sterility.

Examination revealed a mass, the size of a walnut, in the right horn. At the mere mention of operative treatment she consulted at least three other qualified obstetricians and returned to me two months later. The cornual mass was slightly larger, but a soft globular mass, the size of a tangerine, was now palpable on the left side of the uterine corpus. On the recommendation of a consultant of outstanding ability whom she visited, I decided to operate. The condition found was startling. The mass in the right horn was a dense

*Presented at a meeting of the Chicago Gynecological Society, March 16, 1951.

accumulation of tissue which biopsy showed was normal uterine muscle. Arising from the left anterior uterine wall, below and mesial to the insertion of the Fallopian tube and round ligament, was a translucent sac containing a 3 months' healthy-looking ovum. In the light of subsequent experience this pregnancy might have gone to full term, the sac harboring the placenta and the fetus developing in the uterine cavity, though spontaneous rupture would more likely have occurred. Be that as it may, the sac was opened, the ovum removed, and the uterine incision closed after a strip was taken for microscopical study. Convalescence was uneventful. Twenty months later, at age 43 years, cesarean section was productive of a healthy full-term baby and revealed a uterus without trace of the former sac or muscle mass in the right horn. There have been no subsequent pregnancies and no menstruation in the past three years. A recent pelvic examination revealed a normal status.

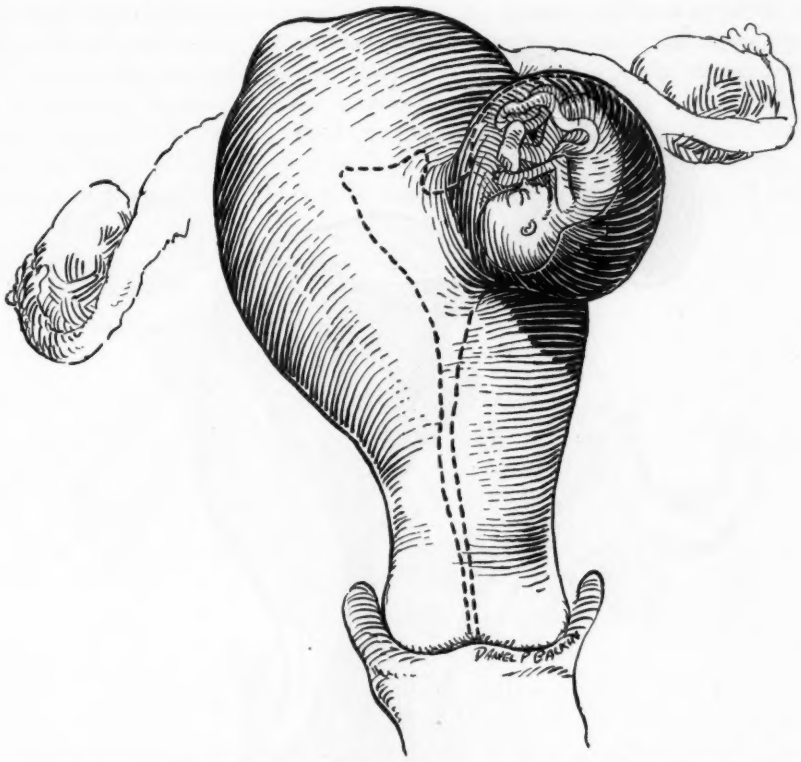

Fig. 1 (Case 1).—Diverticulum of left anterolateral wall of 3 months pregnant uterus. Removed at operation. Cesarean section, twenty months later, revealed no evidence of previous surgery.

The second case is the first of three sacculations at full term and concerns a primigravida delivered spontaneously in September, 1941, after a normal pregnancy. Her physician attempted to remove the placenta manually and instrumentally, consuming a period of about eight hours. He succeeded in recovering only small fragments in the effort. Under the circumstances, hysterectomy was chosen as the safest procedure. The hospital pathologists reported "postpartum uterus with defect in the right upper horn, mesial to the tube and round ligament; thickness of sac 1 to 2 mm., myometrium elsewhere 2.4 to 3 cm." Although the placenta was contained almost entirely in this translucent sac, the labor was normal and no excessive bleeding occurred during the third stage or during the futile efforts to recover the trapped placenta.

The second patient with sacculation at full term was first seen in February, 1947. This patient sought relief for low abdominal pain, scanty, irregular, and somewhat infrequent

menstrual periods, and inability to conceive during thirteen months of marriage. She was a healthy-looking, cooperative patient, aged 21 years. She had had a pelvic laparotomy at age 16, at which time the appendix was removed. When she came to me she was concerned mainly with her fear of sterility.

Examination revealed a small, hard uterus deviated to the left and adjacent to a softer globular mass on the right side, the size of a tennis ball. Operation was performed on April 8, 1947. The right tube and ovary were adherent to one another and to a uterus about two months pregnant. On the left side, a small uterine corpus with normal tube and ovary were found lying inferior and anterior, free of adhesions. While the abdomen was open, vaginal examination revealed a single cervix, apparently belonging to the pregnant uterus. The adherent adnexa on the right side were freed and the abdomen closed. Convalescence was uneventful and the patient went into spontaneous labor seven months later on Nov. 13, 1947.

Fig. 2 (Case 2).—Full-term uterus removed several hours after unsuccessful efforts to remove placenta from uterine sacculation in fundus of uterus.

Case 4 was similar, but placenta was removed vaginally, and the uninjured uterus was spared.

After a good though futile test of labor, a low cervical cesarean section was easily accomplished. The corpus on the left side was very deeply cyanotic, had enlarged slightly during pregnancy, and was probably interfering with the successful progress of labor. After the placenta was removed and the uterus sutured, inspection revealed a very thin, flaccid, wrinkled area at the vault of the uterine fundus. This was an empty, collapsed sac continuous with the thick corpus. Convalescence was uneventful. The second cesarean section on this patient, performed the following year, revealed no thinning of the uterine wall.

My fourth case occurred in a healthy young primigravida who was first seen on Nov. 24, 1947, two months after her last menstruation and two weeks after a short period of spotting. Bimanual examination revealed a very wide early pregnant uterus, recorded as probably bicornuate. Her estimated date of delivery was July 9, 1948, and on July 12 she was easily delivered of a baby presenting by the breech. Ergotrate was administered intravenously, and shortly thereafter expression of the placenta was attempted without success. Exploration revealed about seven-eighths of the placenta trapped within a sac arising from the right side of the uterine fundus. The connecting aperture did not quite admit two fingers. While an assistant controlled the sac through the abdominal wall, several efforts to remove the placenta with ring forceps failed because the instrument failed to hold the placenta in its grasp. Bleeding was moderate. The patient was kept under very light anesthesia until an ovum forceps, the concave surfaces of which are armed with small teeth, was obtained. After deeper anesthesia was resumed, the cervix was grasped with ring forceps, the assistant pushed the sac downward, and many efforts succeeded in removing successively larger placental masses and membranes until the sac was emptied. At this time the neck of the sac admitted two fingers. At the conclusion of this unusual third stage, bimanual examination, with one hand in the uterine cavity, established the fact that his case was almost parallel to our second case, both characterized by sacs of unbelievable thinness.

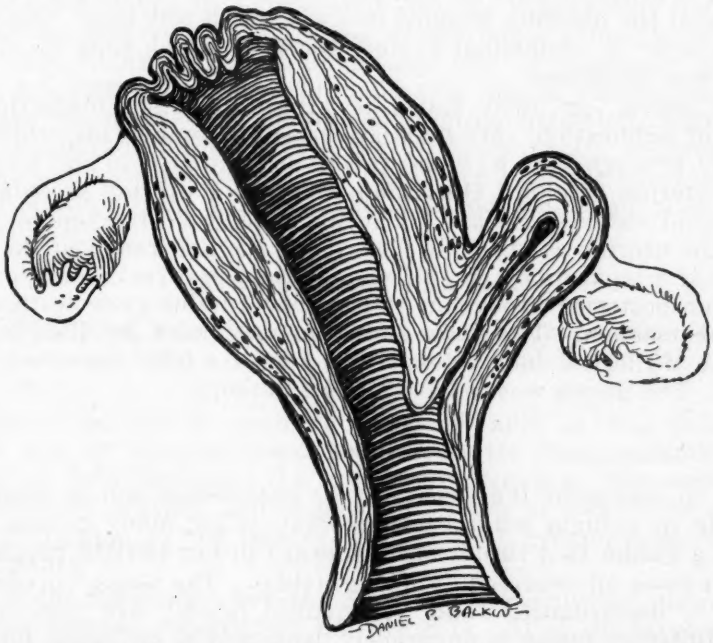

Fig. 3 (Case 3).—Sacculation without a neck in fundus of bicornuate uterus found at cesarean section.

The puerperium was uneventful. Three months after delivery a roentgenogram, after Lipiodol instillation, disclosed a uterus markedly bicornuate with no other irregularity to indicate previous sacculation.

Review of the Literature

The six cases reported previously to mine represent a traumatic and tragic obstetrical picture. In 1901, Freund[5] operated on a primigravida in the twelfth month of pregnancy, five months after spontaneous rupture which

occurred through a uterine sacculation. The fetus was removed, the uterus repaired, and the patient recovered.

In 1904, Schickele[5] attended a patient who had had two spontaneous deliveries at or near full term. In this third pregnancy, pains began when anticipated and continued for several weeks without dilatation or effacement. Intrauterine death occurred. In the eleventh month of pregnancy, sufficient dilatation was accomplished with hydrostatic bags to perform embryotomy. Autopsy on the mother disclosed sacculation of the uterine fundus.

In discussing Schickele's case, Straude reported a 38-year-old gravida xii who was admitted to the hospital undelivered and bleeding in the eighth month of pregnancy with a dead fetus and peritonitis. A Porro operation revealed a macerated fetus lying in a uterine sacculation. Straude reported a second case which concerned a gravida viii at full term. Cesarean section for arrested labor disclosed a sac large enough to harbor twins and a fused placenta. Both of Straude's patients died.

Hellendall's case, in 1905, presented many interesting features. A 42-year-old gravida xii had abdominal pain and uterine bleeding in the third month, which subsided until the fifth month, when she developed sharp abdominal pains and fever. She delivered a 24-cm. fetus nineteen hours later, but prolonged effort to express the placenta failed. Attempts at manual removal revealed the placenta trapped in a sac which was torn. Death followed three hours after an abdominal hysterectomy, at which time the diagnosis of sacculation was confirmed.

Shaw's article,[3] in 1930, failed to arouse sufficient obstetrical interest at the time of publication. My first case closely resembles his, which describes a 31-year-old primigravida who had severe abdominal pain and a cystic swelling in the uterine fundus. Operation revealed a uterine sacculation which the fetus could enter and leave. The placenta was attached to the normal portion of the uterine cavity. He incised the sac and removed the conceptus. At the time of a laparotomy on this same patient two years later, only a slight midline anteroposterior groove in the uterine fundus gave testimony of the previous phenomenon. The findings in this case were ascribed to failure of fusion of the Müllerian duct. Hess's two cases are fully described in a recent publication. The uterus was removed in one patient.

Etiology

Efforts to determine the cause of true sacculation end in frustration. It is impossible to explain why a woman may enjoy many normal deliveries, only to fall a victim to a ruptured uterine sac in her twelfth pregnancy.

My four cases all occurred in primigravidas. The terms "predisposition," "tendency," "disturbance," and "congenital faults" are mere generalities. Defective Müllerian fusion is apparently disproved in my cases, for in none of them did the sacculation occur in the midline.

An attractive theory would be that, at the time of implantation of the ovum, there is an exaggeration of the normal trophoblastic destruction of the maternal cells. This invasion, then, may extend beyond the usual confines of the decidua and weaken the myometrium at the point of implantation. With the progress of pregnancy, it may be postulated that this compromised area sacculates.

Rudolph[2] insists that the Piskacek sign and *grossesse angulaire* are functional and transitory phenomena. Perhaps these are early forms of sacculation due to the "villification" of uterine wall, which, on rare occasions, may persist and develop into large diverticula.

A study of the etiology of sacculation in other viscera is not illuminating. Herniation along the paths of blood vessels is an ingenious theory. Traumatic, degenerative, and inflammatory processes and faulty innervation have been considered as possible causes. DeLee's[4] textbook devotes a short paragraph to "diverticula" of the pregnant uterus, and mentions one of the cases I have quoted.

I believe that the processes involved in attachment of the ovum to normal endometrium, characterized by "eating the epithelium" and "enzyme action which dissolves, absorbs, and destroys the decidua," are the basic factors in sacculation, when these processes pathologically attack uterine muscle.

Diagnosis

An extensive variety of pelvic pathology is involved in early differential diagnosis. Pregnancy associated with uterine anomalies will simulate sacculation. Only in Hess's second case was the condition suspected.

True sacculation probably always begins very early in pregnancy as was proved in Shaw's[3] and in my first case. It is, therefore, most important to study carefully the irregularities in uterine contour so frequently found at the time of the early first prenatal examination. Persistent low abdominal pain in early pregnancy in a previously healthy woman may not be ignored and the patient assured that it is one of the minor ailments of pregnancy. Although frequent abdominal examinations late in pregnancy might reveal an existing sacculation, it is more probable that the sac blends with the normal portion of the corpus in such a manner as to escape detection. Soft tissue technique roentgenography might prove useful for diagnosis, especially in those cases in which threatened uterine rupture is even remotely suspected. Manual exploration of the uterine cavity in the third stage of labor is an exact diagnostic procedure.

Treatment and Prognosis

The difficulty of establishing a plan of treatment arises from the fact that no case, except Hess's, has ever been diagnosed before delivery, laparotomy, or autopsy.

Our fourth patient is young and fertile, and, as was shown by hysterography, has an arcuate uterus with complete disappearance of the sac which trapped the placenta at the time of her delivery. Her next pregnancy must be carefully studied, and if sacculation can be demonstrated, cesarean section is preferable to the risk of repetition of instrumental removal of a trapped placenta.

Great is the dilemma when the condition is discovered only at the time of attempted manual removal of the placenta. It is doubtful whether the placenta can often be recovered without tearing the sac, and though an attempt may be made, laparotomy must be anticipated.

If an intelligent, cooperative patient complains of severe, prolonged low abdominal pain, even early in pregnancy, and uterine irregularity and uterine tenderness can be demonstrated, laparotomy may be justified. Operation may reveal a diverticulum in a pregnant uterus or one or more of a long list of other pathological lesions. The immediate fate of the conceptus must be decided by the operator. Many weeks of anxiety must be accepted if the ovum is undisturbed. The possibility of successful delivery after viability must be weighed against the serious results of dystocia, rupture, abortion, inversion, and placental entrapment.

Summary and Conclusions

1. Four cases of diverticula of the contractile portion of the pregnant uterus are presented.

2. It is emphasized that these are true sacculations of the uterine corpus and not comparable to the "functional sacculation" described in the general obstetrical literature.

3. The literature on this rare but important pathological obstetrical entity is reviewed.

4. A postulate is offered that this condition may occur because of an exaggeration of the normal implantation phenomena with weakening of the adjacent uterine musculature and resultant sacculation as pregnancy progresses.

5. To date, the diagnosis of true sacculation of the contractile portion of the pregnant uterus has not been made prior to delivery, laparotomy, or autopsy, except in Hess's case. Suggestions which may allow earlier diagnosis are offered.

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Discussion

DR. B. I. COOPERSMITH.—I want to commend Dr. Rubovits on his astute clinical observations and for his wisdom in bringing this intriguing obstetrical condition to our attention. As long as sixty years ago, and probably before that, the question as to whether sacculation or diverticulum of the pregnant uterus actually existed was hotly debated. In recent years other reports allow no doubt that the condition occurs.

To the list already presented I wish to add an unusual case of bilateral sacculation of the uterus.

This patient, a 19-year-old primigravida, entered Wesley Memorial Hospital on Nov. 23, 1950, at 38 weeks' gestation. Her prenatal course had been normal. After 12 hours of irregular uterine contractions she was discharged as having false labor. The following day she was readmitted, because of spontaneous rupture of the membranes with loss of considerable fluid. The fundus was 27 cm. high, the fetus in occipitodextra anterior position at minus one station with an uneffaced closed cervix. On Nov. 25, 1950, vaginal examination revealed the same findings and fetal hair was obtained to prove rupture of the membranes. The patient was not in labor and prophylactic penicillin was begun and administered daily. On November 27 Pitocin, 1 minim, was given every 20 minutes in an attempt to initiate labor. This was discontinued after three doses because the resident physician noted a "ballooning-out" of the uterus without true contractions. For the rest of that week, she experienced irregular uterine contractions and was moved from the maternity floor to the labor rooms on three occasions because of suspected true labor. The cervix remained long and closed.

One week after admission, in an attempt to initiate more effectual uterine contractions, intravenous Pitocin was given by slow drip. Under this stimulus very unusual contractions were noted: intermittently the uterus rose markedly toward the anterior abdominal wall, and seemed to balloon out. This phenomenon lasted about 20 seconds and then sudden relaxation

ensued so that the uterus returned to its relaxed state within five seconds. There was no pain associated with these contractions. A tentative diagnosis of sacculation of the uterus was made.

A low cervical cesarean section was performed under general anesthesia with delivery of a 6 pound, 4 ounce infant through a longitudinal incision in the lower uterine segment. The placenta was removed manually from the anterior wall of the corpus. Examination of the uterus after delivery revealed two thinned pouches or sacculated areas on the posterior wall symmetrically situated just behind the insertion of the uterine tubes. These sacculated areas measured approximately 2 mm. in thickness and 7 cm. in diameter. With slight digital pressure these areas could be dimpled inward toward the uterine cavity almost like a paper bag. The rest of the musculature of the uterus was normal but poorly developed and there was a thin ridgelike formation in the uterus anteriorly in the midline. No definite septum was demonstrated inside the corpus.

The uterus and abdomen were closed in the usual manner and the patient made an uneventful recovery. The corpus felt normal to palpation at six weeks post partum.

DR. A. LASH.—About 20 years ago I was having a run of advanced abdominal pregnancies on my service at Cook County Hospital and during this period I operated upon a woman with the clinical picture of an extrauterine pregnancy with an amenorrhea of sixteen weeks. To my surprise, I found a marked ballooning and thinning of the left cornu so that the fetus was visible. In view of the symptoms and findings I opened the uterus and emptied this sac. After removal of the contents, the uterine wall gradually resumed its normal thickness.

Five years later, again at Cook County Hospital, I operated upon a woman supposedly 20 weeks pregnant with the clinical picture of an extrauterine pregnancy. On opening the abdomen, I found a blisterlike sacculation of the left horn of the uterus with the fetus visible. Being fortified with my previous experience, I gently massaged the corpus and observed the uterine wall thicken without disturbing the pregnancy. I closed the abdomen and the woman went to term and delivered a normal baby vaginally.

My third experience was in 1938 when I was asked to see a 28-year-old primigravida, 24 weeks along in her pregnancy, with very severe pain in the right lower quadrant which radiated down the right thigh and which persisted for several hours. During this painful period she vomited twice. She had had a previous similar attack three weeks before, when the pain was knifelike in character and on going to the bathroom she fainted. She was revived and the pain gradually subsided until the present attack. On admission to the hospital her temperature was 99° F., pulse 100, blood pressure 136/96, general condition appeared good. Abdominal examination found exquisite tenderness in the right lower quadrant with an indefinite soft mass. Red blood cells 3,450,000; hemoglobin 70 per cent; white blood cells 9,400.

Diagnosis was made of probable extrauterine pregnancy. On opening the abdomen, I found a marked thinning of the right cornu of the corpus uteri rendering the fetus visible. I massaged the uterine wall and observed it thicken. I closed the abdomen. She had no recurrence of her difficulty and delivered vaginally at term a 6-pound, 12-ounce baby.

In 1945, she had a spontaneous abortion at ten weeks, which required evacuation of placental remnants. At this time no abnormality of the uterine cavity was found.

This very interesting phenomenon of abnormal physiology of the uterine muscle is not common but it is important to recognize its characteristics so that the pregnancy is preserved in spite of the alarming clinical picture. I have no suggestion as to how to differentiate it from an extrauterine pregnancy without exploratory laparotomy.

DR. HARRY BENARON.—I recall first seeing this clinical entity in 1938 on the service of the Chicago Maternity Center. I believe it to be merely an altered physiology of the uterine musculature; the first case excited me greatly—several exceedingly thin, balloonlike areas appeared in the corpus uteri—measuring from 6 to 7 cm. in diameter. They would appear and disappear with the uterine contractions. Dr. Joseph B. DeLee was

consulted and he sent the late Dr. Rudolph out to take a photograph. The patient delivered easily without incident. The condition is not as uncommon as would appear from the dearth of literature on the subject. Prenatally these sacculations can be seen during normal Braxton Hicks contractions. My last patient was an infertility case who became pregnant after surgery for resection of polycystic ovaries. This patient had two sacculations involving both sides of the corpus uteri 10 to 11 cm. across. Her labor was characterized by inertia, but she was delivered from below easily. As I have seen the condition I would not consider it an indication for delivery from above per se.

DR. RUBOVITS (Closing).—Apparently I failed to emphasize the very great clinical difference between a gourdlike uterine sacculation with a very narrow neck and the crater-like sacculation which represents a less serious obstetrical problem, such as was described this evening by Drs. Coopersmith, Lash, and Benaron. To assume the attitude, in the words of one of the discussants, employing the phraseology of a famous authoress, that "a sac is a sac is a sac," ignores the fact that the former is fraught with the very great danger of entrapment of all or any part of the conceptus and that the latter is relatively harmless and much less likely to cause dystocia. Confusion in determining the etiology is complicated by the fact that the erratic behavior of uterine muscle may result in both sacculation and localized excessive thickening of the uterine wall at the same time, as illustrated by the specimen which I have presented.

If, in the future, fewer perforations and fewer ruptures of the pregnant uterus of unknown origin are found at autopsy, I shall feel that this presentation has been justified.

ACUTE RENAL INSUFFICIENCY

Physiopathology and Treatment, With Presentation of Cases Occurring on an Obstetric Service

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A KNOWLEDGE of the physiopathology, the clinical symptoms, and management of acute renal insufficiency is of great importance to physicians in the field of obstetrics and gynecology, as this condition may follow the hemorrhagic accidents that occur in connection with pregnancy or parturition, or may result from sepsis, either postpartum or postabortal. A considerable amount of clinical, physiological, and experimental data has accumulated concerning this distinctive renal insufficiency, especially since Lucke[1] reported his observations of war casualties during World War II. The terminology has not as yet been standardized for the syndrome of anuria or extensive oliguria, thus the terms "hemoglobinuric nephrosis," "shock kidney," "kidney lesion of crush syndrome," and "lower nephron nephrosis" are all referable to the pathologic condition characterized by degeneration and necrosis of the entire nephron. The term "acute tubular necrosis" has been used by Bull[2] in an excellent paper presenting renal function studies on these cases.

Since the clinical entity with which one has to deal is acute renal insufficiency on a functional basis, we believe that this is the best name, for practical purposes, with which to label these cases. The anatomic situation characteristic of this condition is acute tubular necrosis; the functional situtation is one of anuria, or oliguria, with retention of nitrogenous waste products in the blood stream at abnormally high levels. For recovery it is necessary that the tubular necrosis be followed by regeneration of the renal tubular epithelium, and this by consequent return of renal function. Renal function studies[2] have shown evidence of gross tubule dysfunction and extreme diminution in renal blood flow, and, in the fatal cases, the uniformity of functional disturbance was paralleled by the characteristic pathologic picture, acute tubular necrosis.

The etiological factors in cases of anuria or severe oliguria may be divided into two major groups. The first, which has been referred to as the "prenephron" group, includes (1) hemorrhage with prolonged shock, (2) dehydration, (3) severe anemia other than that subsequent to acute hemorrhage, and (4) cardiac failure. The second, the group consisting of renal causes, includes (1) acute tubular necrosis, due to (a) transfusion with incompatible blood,

(b) alkalosis, (c) burns, (d) sepsis, and (e) exogenous toxic substances such as mercury, phosphorus, and the sulfonamides; (f) bilateral acute tubular necrosis, chiefly cortical in distribution, is characteristically found at autopsy in fatal cases of toxic abruptio placentae; (2) glomerulonephritis, (3) malignant hypertension, and (4) pyelonephritis. The last three conditions listed may also have superimposed pre-eclampsia or eclampsia.

As early as 1929 Richards[3] demonstrated with frogs, which had been poisoned with mercury, that the glomeruli remained normal as to blood flow and filtrate, but the filtrate was completely resorbed, presumably by the osmotic attraction of plasma proteins from the lower nephron. Experiments by Hamilton,[4] on dogs, in which he induced ischemia of the kidney, and maintained it for varying durations up to two hours, showed that this resulted in a temporary depression of the urea clearance to zero with recovery in two to three weeks; dogs which had had induced ischemia of the kidney for as long as four hours died, in four to eight days, of uremia. He demonstrated that the pathologic lesion was necrosis of the distal tubule, the glomeruli remaining essentially normal. Lucke[1] Mallory,[5] Bywaters[6] and Muirhead[7] agree that the pathologic lesion is that of severe degeneration and focal necrosis of the loop of Henle and of the distal convoluted tubule; in the more proximal portion of the tubule there may be rupture of the surrounding interstitial tissue or of the venules; the glomeruli remain intact, although the basement membranes may be damaged, as evidenced by thickening.

In the experience of the obstetrician and gynecologist this renal damage is usually the aftermath of prolonged hypotension due to hemorrhage or to severe sepsis in the postabortal or postpartum patient. By what mechanism does the tubule damage occur? Trueta[8] believes the damage results from spasm of interlobular arteries secondary to anoxia. In his animal experiments he demonstrated shunting of blood from cortical nephrons to the juxtamedullary nephrons by reflex mechanisms. In cases of retroplacental hemorrhage Young[9] believes that substances are liberated which cause spasm of the interlobular arteries. Doniach[10] suggests that the vessels of the kidney during pregnancy appear to be hypersensitive to hemorrhage elsewhere in the body.

There is obviously a greatly reduced renal flow in obstetric hemorrhage, with resultant diminution of the oxygenation of renal arteriolar blood, but the decreased renal blood flow would also seem to be due to passive flow of edema fluid through tubular walls into the interstitial spaces, causing edema there, and a resultant increase in the intrarenal tension with some compression of the peritubular capillaries. The kidney is extremely susceptible to anoxia and the oxygen consumption of the kidney diminishes in direct proportion to the decrease in renal blood flow (Dole[11]).

In the management of anuric or oliguric patients the clinician should be cognizant of three important factors in the therapy: (1) disturbance of water balance; (2) alterations in electrolyte balance, especially sodium, potassium, and calcium; and (3) derangement of nitrogen balance. There are four distinct dysfunctional phases in anuric and oliguric patients, and an understanding of the physiologic situation in each phase will determine the therapy of them.

In the first phase, when renal failure occurs from diminished renal blood flow, there is the onset of a usually short-lived anuria, which results from hypotension and oligemia, sepsis, or the other etiological factors mentioned. Treatment calculated to relieve the hypotension and renal oligemia (i.e., antishock measures) must be the primary therapy during this phase, if hypoten-

sion is the immediate cause. Sepsis should be controlled by specific chemotherapy, after determination of the offending organism by stained smear and cultural methods.

In the second phase, the phase of renal insufficiency, the kidneys fail to resume normal function despite improvement of the general circulation (Fig. 1). This phase depends upon the amount and extent of kidney damage and may be short, if the damage is slight, or may continue into fatal uremia if the tubular necrosis is severe and widespread. In this phase the renal blood flow and filtration rate are low, and there is a lowering of the urea clearance, a fixed specific gravity of the urine, and proteinuria and casts may be present. There is azotemia and a decrease of plasma bicarbonate, chlorides, and serum sodium, with a tendency to acidosis and coma. The serum potassium is elevated, which elevation is frequently observed when there is suppression of urine volume, inasmuch as a urine output of 100 to 200 c.c. in 24 hours is inadequate to accommodate the needs for excretion of the potassium supplied to the plasma. This phenomenon of potassium intoxication occurred in the patient to be presented, as evidenced clinically by lack of phonation and weakness of respiratory movements. The treatment in this phase is directed toward replacing the insensible water loss in addition to the volume of urine excreted. Acidosis is prevented by the administration of sodium bicarbonate and ⅙ molar lactate intravenously, or orally if possible. The food intake is maintained by use of a high-calorie, low-protein diet to minimize the formation of nitrogenous products. If hyperpotassemia occurs, the sodium ion in the body, which is antagonistic, is increased, in order to reduce the serum potassium level, by intravenous saline or oral sodium chloride, and/or by the use of gastric lavage as the gastric juice may at times contain as much as 40 milliequivalents of potassium per liter. Electrocardiogram is a very sensitive method of observing serum potassium concentrations, for in several respects the findings associated with low serum potassium concentrations are the opposite of those found in high serum potassium levels. Attempts at stimulation of the kidney by the administration of hypertonic intravenous glucose are usually fruitless since the damaged kidney is unable to respond, hence there is no indication for attempts at renal stimulation, and the use of drugs, such as mercurial diuretics, is specifically contraindicated.

The third phase, early diuresis, follows in eight to twelve days and results in excessive loss of plasma electrolytes. The nephron has not yet completely recovered, although renal blood flow approximates normal. Electrolyte balance is maintained by replacement, with carefully calculated amounts of fluid and electrolytes, of the water and electrolyte substances excreted excessively by the patient. The water loss in 24 hours is the volume of urine excreted plus the insensible loss (usually 1,500 c.c.), to which should be added an estimation of the amount of perspiration, according to the situation and season. The plasma levels of Na, K, and Cl should be determined as often as indicated and an attempt should be made to keep them at nontoxic levels, by replacing, gram for gram, these electrolytes as they may be depleted by the faulty renal excretion. No simple rule can be derived to calculate the potassium needs of the patient in the early diuretic phase, but Bull and associates[2] have found that patients fed on a diet largely composed of fruit from the start of this phase seldom develop clinical evidence of disturbed potassium metabolism. The patients must be watched carefully during the early diuretic phase, as dehydration and shocklike convulsions may occur. The persistence of hypertension, a continued postponement of diuresis, and a low urea clearance and fixed specific gravity of the urine well beyond the time when this phase should normally begin carry a poor prognosis.

The late diuretic phase usually begins twelve to fourteen days after the initial onset of renal insufficiency. During this period residual depletion of function may be noted. The amount of permanent destruction of renal substance can be determined during this phase by use of the urea clearance and *p*-aminohippurate tests.

Clinical Material

We have had five patients with acute renal insufficiency on the Obstetric and Gynecologic Services during the last two and one-half years, three of whom were treated in the last twelve months. The patients were, with one exception, Negro women who were treated by a fairly well-established method which we wish to emphasize. These women all had severe oliguria or anuria for longer than six days, and consultation by members of the medical service brought concurrence in our diagnosis, and suggestions regarding treatment. An important portion of the blood and urine chemical studies were very generously carried out in the laboratories of the Department of Medicine of the Detroit Receiving Hospital.

This group of patients consisted of three who had abruptio placentae with severe hemorrhage, one case of pre-eclampsia with edema and oliguria, and one case of septic criminal abortion. There was one fatality in this series and autopsy verified our clinical diagnosis of extensive renal tubular necrosis.

Inasmuch as all cases were treated similarly and therefore detailed case studies would be repetitious, we present the latest case and also brief abstracts of our one fatal case, and the case of pre-eclampsia without abruption of the placenta (Case 4).

CASE REPORT.—S. M. (No. 110893), a 31-year-old white woman, gravida viii, para vii, whose last normal menstrual period was Jan. 11, 1950, and expected date of confinement was Oct. 18, 1950, was admitted to the Obstetric Division of the Herman Kiefer Hospital at 11:25 P.M., Sept. 13, 1950, in early labor. She gave a history of slight vaginal bleeding for seven hours. The admission examination revealed a blood pressure of 115/70 and a full, regular pulse of 80 per minute. The respirations were 20 per minute. The uterus was the size of an eight months' gestation and the fetal heart rate was 140 per minute. There was evidence of slight vaginal bleeding. Blood was drawn and typing and cross-matching were immediately performed. The patient was type O, Rh negative. She began to have profuse vaginal bleeding at 3:00 A.M. on Sept. 14, 1950. Upon examination she was found to have a thready, rapid pulse, and the blood pressure was not obtainable at this time. Intravenous fluids and nasal oxygen were started. The uterus was noted to be tense, and of a boardlike firmness, there being no palpable fetal outline. Thirty minutes later she delivered spontaneously a 2,665 gram, flaccid, cyanotic female infant who survived. At this time the blood pressure was 130/80, and the pulse was 120 per minute. The placenta was delivered by simple expression, and the presence of a large, fresh, retroplacental, intradecidual (as subsequent histologic study revealed) hematoma was noted. The estimated blood loss at the time of delivery was 400 c.c. The blood pressure remained stabilized at 130/70 and the pulse was 110, regular and full. The patient was alert and aware of her surroundings.

She was found to be bleeding from the vagina in more than a normal amount at 5:00 A.M., or one hour and thirty minutes after delivery, and was taken to the delivery room and examined, but inspection of the cervix and vagina failed to disclose any bleeding site. The blood pressure was not obtainable, the pulse was 160 per minute, weak and thready. The uterus was neither explored nor packed at this time since the resident on duty assumed that this was practically never necessary. A vein was cut down upon, cannulated, and 1,500 c.c. of whole, type O, Rh-negative blood were given to the patient under slight pressure. She continued to bleed and the blood pressure remained unobtainable. The uterus was then manually explored and packed, which controlled the bleeding. She was given another 1,000 c.c.

of whole blood, type O, Rh positive (there was no Rh-negative blood available at the time in the blood bank), following which the pulse became stronger, full, and 120 per minute. Whether this incompatibility of the Rh factor played a major role in the resultant nephron damage one can only conjecture, but the prolonged hypotension and oligemia, we feel, were the major factors in bringing about the azotemia and anuria. The blood pressure now was 90/60, pulse 120 and full and regular. Following the administration of this last blood transfusion she became alert and no longer was cold or clammy. The hemoglobin at this time was 58 per cent, and the red blood count was 2.8 million. A catheter specimen of urine (atraumatically secured) was grossly bloody. Twelve hours after delivery, because of persistent oliguria, 1,000 c.c. of 5 per cent glucose and 1,000 c.c. of 1/6 molar lactate were administered intravenously, and were followed in two hours with 500 c.c. of whole, type O, Rh-negative blood. The urinary output for the first 24 hours was 224 c.c., with a total intake of 5,000 c.c. At this point we are at the end of the first phase of this syndrome in this patient and thus treatment for the second phase begins. Fig. 1 demonstrates the fluid intake and output, and the electrolyte balance during the remainder of the patient's hospital stay.

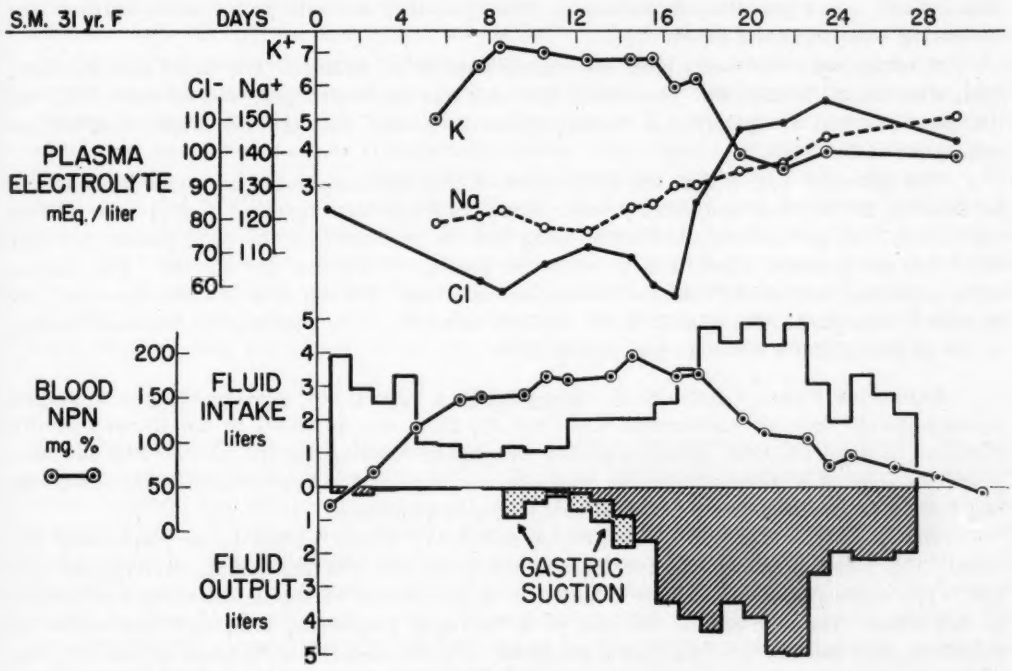

Fig. 1.

Fig. 1 shows that the phase of renal insufficiency lasted until the eleventh day; during this time there was anuria and the fluid intake, although high at first, was subsequently restricted to approximately 1,000 c.c. daily. The chloride level diminished, but the potassium level increased and reached the level of intoxication on the eighth day, at which time the patient evidenced respiratory difficulty, difficulty in phonation, and marked generalized weakness. Sodium was administered and intermittent gastric suction instituted to remove some of the potassium. The blood nonprotein nitrogen rose during this time but remained rather stabilized at 150 mg. per cent.

Early diuresis began on the eleventh day, and the fluid intake accordingly was increased proportionately to offset excessive urinary secretion of water and electrolytes. The gastric suction continued to aid in offsetting the hyperpotassemia.

The onset of the late diuretic phase, as noted on the chart, occurred on the fifteenth day, when there was an output of 3,600 c.c. and a corresponding increase in fluid intake. The

plasma chlorides level reached a new low and thus correction of the electrolyte balance was necessary. The urinary output was profuse during the next week and thus the plasma potassium level diminished as the sodium and chloride levels reached normal in the plasma. The prevention of hypopotassemia by oral administration of potassium chloride, 6 to 8 Gm. daily, should be routine procedure during this phase of therapy. The blood nonprotein nitrogen returned to a normal range by the twenty-eighth day, as did the plasma electrolytes. The specific gravity of the urine, even in a concentration test, was never above 1.008. The urea clearance was 43 mg. per cent of normal on the twentieth day, while eight days later, on the day of discharge from the hospital, it was 38 per cent. A phenolsulfonphthalein test showed 40 per cent retention for five minutes and 5 per cent retention at the end of thirty minutes. (The normal of our laboratory is 35 per cent retention at five minutes and 0.5 per cent at the end of thirty minutes.)

The patient was seen six weeks after delivery, and complained of weakness, headaches, dizziness, and generalized paresthesia. She had had no menstrual period, thus the possibility of pituitary necrosis was entertained. A catheterized urine specimen showed slight glycosuria, a trace of albumin, and a specific gravity of 1.015. The blood urea nitrogen was 12 mg. per cent. There was a persistent hypertension, 160/100, which was interpreted as an ominous sign indicating some cortical necrosis.

A return visit two weeks later showed the same urine findings. Her blood pressure, however, was normal at 120/80. She stated that she was much stronger, had no headaches, but dizziness occurred frequently. A normal menstrual period, lasting three days, occurred one week prior to this visit.

The last visit was on Jan. 29, 1951, at which time the patient had no complaints and was performing all her own household duties. Renal function tests revealed a glomerular filtrate rate of 78.7 c.c. per minute, the normal being 120 c.c. per minute. The renal plasma flow was 481.8 c.c. per minute, which is well below the normal of 600 c.c. per minute. The tubular mass, equaling the average of two determinations was 77.3 mg. per minute, corrected for mannitol absorption (the normal is 70 mg. per minute). The values show residual damage to the glomeruli and a lowered renal plasma flow.

Report of Fatal Case.—E. J. (No. 95944), a 28-year-old, gravida vi, para v, Negro, whose expected date of confinement was June 30, 1948, was admitted to the Herman Kiefer Hospital on June 22, 1948, giving a history of vaginal bleeding for five hours. She had been under the care of a private physician who was treating her for hypertension. She stated she had felt no fetal movements for several hours prior to admission.

The admission examination showed an acutely ill Negro woman in no respiratory distress. The blood pressure was 108/68, and the pulse was 132 per minute and regular and full. The respirations were 24 per minute. A small amount of vaginal bleeding was present at this time. The uterus was the size of a full-term pregnancy, firm, and very tender to palpation, especially in the right lower quadrant. No fetal heart sounds could be heard by any of the numerous examiners. Shortly after admission the patient went into shock, having a blood pressure of 80/40 and a rapid, thready pulse. To combat the shock, 1,000 c.c. of Rh-negative, type O blood were immediately given under pressure. During this time the patient went into active labor and six hours after admission she delivered a full-term, 3,860-gram, stillborn, nonmacerated, male infant. The estimated blood loss at the time of delivery was 1,200 to 1,500 c.c.

Two hours after delivery, however, she again had a fall in blood pressure to 80/60, at which time the hemoglobin was found to be 49 per cent and the red blod cell count was 3 million. She was given another transfusion of 500 c.c. of type O, Rh-negative blood. She was given, during the first eight days, four more blood transfusions and her fluid intake was limited to a total of 1,500 to 2,000 c.c. daily. The patient was practically anuric and during the first eight postpartum days the total urinary output was 800 c.c. On the tenth and eleventh days post partum the urinary output remained approximately 100 c.c., and there was a "fixed" specific gravity of 1.011. The blood nonprotein nitrogen level gradually rose and she developed uremic pericarditis on June 27, at which time the blood nonprotein nitrogen was

94 per cent. There was a persistent hypertension of 180/100. The electrolyte balance was maintained, the fluid and electrolyte intake being guided by daily calcium, potassium, phosphorus, and sodium blood studies. She was digitalized, but despite all this, the blood nonprotein nitrogen rose to 480 mg. per cent 28 days after admission. She died 58 days after admission and sections of the kidney showed nephrosis of the lower nephrons and bilateral cortical necrosis. She also had uremic pericarditis.

CASE 4.—This woman, a nonregistered Mexican, was malnourished and moderately underweight for her height and age. She had not gained weight excessively during pregnancy, and was referred to the Herman Kiefer Hospital by her family physician because of the onset of headaches, nausea and vomiting, and swelling of the eyelids, face, and legs. She had taken sulfathiazole for urinary-tract infection for six days one week prior to entering the hospital. On admission her blood pressure was 170/110, and there was a 3-plus albuminuria, marked edema of the eyelids and face, a 3-plus pitting pretibial edema, and oliguria (she excreted 90 c.c. of urine the first 24 hours following admission). Ophthalmoscopic examination revealed bilateral haziness of the optic disc margins (which was thought to represent mild papilledema), and slight A-V nicking but no hemorrhages nor exudates. The red blood cell count was 5.3 million, hemoglobin 84 per cent, hematocrit 35 per cent, blood nonprotein nitrogen 42 mg. per cent, serum chlorides 662 mg. per cent. A careful fluid and electrolyte balance was maintained. Under bed rest, sedation, and general supportive care the blood pressure averaged 160/110, the albuminuria continued at 2 plus, and the average daily urine output was about 600 c.c.; no sulfonamide crystals were found, but occasional hyaline casts were present. She vomited a worm (*Ascaris lumbricoides*) 48 hours after admission. The edema persisted, she vomited nearly every day in small amounts, and the uterus became very sensitive and contractile on the tenth day following admission. On the thirteenth day, following a few hours of labor, she spontaneously delivered a 4 pound, 11 ounce, living infant who survived. Following this, diuresis occurred, and the blood chemistry values returned to normal and the edema disappeared. She was discharged nine days post partum at which time her blood pressure was 128/98, there was no albuminuria, and she was greatly improved.

Comment

The prevention and rapid treatment of postpartum hemorrhage by the proper management of the placental stage of labor and prompt blood replacement receive too little emphasis in obstetric care and in our teaching at the present time. This is particularly true in cases of abruptio placentae (in which there may be some hemorrhagic diathesis) occurring in hypertensive women. Proper handling of the patients will reduce the incidence of postpartum hemorrhage to less than one per cent. Dieckmann and associates[12] have shown the importance of slow delivery of the fetus in the management of the placental stage, and how this permits complete and relatively bloodless separation of the placenta and its ready expulsion by the uterus. Postpartum hemorrhage is a problem which will always be with us. Prompt recognition of such bleeding, no matter how slight, and its immediate and adequate control and blood volume replacement are of paramount importance. The common error of underestimation of the amount of blood loss, especially in those cases in which there is a constant, small, vaginal seepage, accounts for a large portion of maternal deaths due to hemorrhage. If all efforts at stopping the uterine bleeding fail, then the uterus should be packed, by hand, with gauze strips which have been lightly "sugared" with pulverized crystalline sulfanilamide. The experience with the use of such packing at the Herman Kiefer Hospital in the past three years has been good, and there has not been any instance of subsequent sepsis.*

*One should be careful, however, not to overpack the uterus as this defeats the purpose of the pack by distending the uterus and thus "holding open" the source of the bleeding.

The patients having sepsis can in most instances be successfully treated with adequate doses of the antibiotic specific for the offending organism, in addition to the usual supportive measures. We admit to the Detroit Receiving Hospital a fair number of postabortal septic patients, many of whom are near death on admission. However, with the prompt institution of specific antibiotic therapy, blood transfusions, intravenous fluids, and nasal oxygen, our results have been most favorable.[13]

Once the condition of oliguria or anuria has developed, a definite regime of therapy and maintenance of electrolyte balance must be instituted; namely, (1) Insensible water loss should be replaced according to the situation and season, plus urinary excretion loss with isotonic sodium chloride and 5 per cent glucose in Ringer's solution if oral feedings are not possible. (2) A high-caloric, low-protein diet which includes generous quantities of fruit and/or fruit juices should be given. (3) Early ambulation is desirable. (4) Daily blood studies to include plasma sodium and chlorides, nonprotein nitrogen, CO_2 combining power, and, if possible, serum potassium should be made. (5) If serum potassium determinations are not possible, frequent electrocardiograms will aid in determination of serum potassium concentrations. (6) Hypopotassemia can be benefited by the use of potassium chloride by mouth, 2 Gm. twice daily. (7) Hyperpotassemia is combated by use of oral sodium chloride or sodium bicarbonate and/or intravenous isotonic sodium chloride solution. Gastric lavage with suction may be advantageous in some cases. (8) Determination of daily urine volume, specific gravity, and pH of the urine is mandatory. (9) Urea clearance should be determined after diuresis has begun. (10) The blood pressure should be recorded twice daily. The overenthusiasm of some to stimulate renal function by use of hypertonic intravenous glucose solution is not recommended. The therapy of acute renal insufficiency as used by us has not included splanchnic nerve block to counteract local renal vasospasm since once anuria or oliguria is established splanchnic block or spinal anesthesia will not alter the course of the disease.[2] Procedures to eliminate nitrogenous waste products such as peritoneal irrigation or use of the artificial kidney have not been employed, although both procedures will aid in eliminating nitrogenous waste products until the kidney has recovered its function.

Summary

1. A series of five cases of acute renal insufficiency is reported. Four of the patients survived. In the one case in which thorough studies were made, there was residual renal damage, as determined by para-aminohippurate and mannitol tests. The one fatality occurred as a result of bilateral cortical necrosis, the patient surviving for 58 days following delivery.

2. Acute renal insufficiency, resulting from the renal ischemia which is part of the shock following hemorrhage, is as preventable as is the shock itself. Thus adequate management of the placental stage and the hemorrhagic accidents of pregnancy, with the prompt relief or prevention of shock by blood replacement, are the means of prevention of this dangerous complication in obstetric cases.

3. The treatment of postpartum and postabortal infections with broad spectrum antibiotics has in our hands been very successful, and the oliguria or anuria (on a toxic basis) which may occur in these cases requires careful management.

4. The oliguria or anuria which may be a part of severe pre-eclampsia and eclampsia requires adequate study of the blood electrolyte levels and fluid loss in order that these may be properly maintained during the period of renal insufficiency.

The authors wish to express their appreciation of the consultations and help given by Dr. Lloyd T. Iseri, of the Department of Medicine, and for the work done on these patients by Drs. Edwin F. Snider, Richard C. Ashcom, E. Clark Gillespie, John Maunder, Charles L. Schneider, and Nicholas J. Kohlerman, all one-time senior or assistant resident obstetricians at the Herman Kiefer Hospital. To Mrs. Jerry Chesney, for her preparation of the chart, our thanks are also hereby extended.

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THE RESPONSIBILITY OF THE OBSTETRICIAN TO THE FETUS

I. An Analysis of Fetal and Neonatal Mortality in 10,000 Deliveries

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MATERNAL mortality rates are now so low that from the standpoint of preservation of life the infant rather than the mother has become the primary concern of the obstetrician. In 1949 the maternal mortality rate in the United States of America was less than one per thousand. Six states had rates as low as 0.4 per thousand and many more had rates comparable to those of the leading medical centers. When maternal death rates are so low, most of the deaths are not directly related to pregnancy. At Brooke Army Hospital there have been five maternal deaths* in the last 10,000 deliveries; one due to meningitis (due to therapeutic accident), one to chronic brain abscess, one to cerebral hemorrhage from congenital aneurysm, one to acute yellow atrophy of the liver, and one to eclampsia.

Although maternal death from obstetric causes is approaching the irreducible minimum, stillbirth and neonatal loss remains high. The combined stillbirth and neonatal mortality of 5 per cent in the United States represents a loss of over 150,000 lives annually. In 1949 one out of 20 mothers endured pregnancy without the reward of a living child. The day of birth remains the most dangerous single threat to life an individual ever faces. War is safe by comparison. The analysis of fetal and neonatal mortality provided in this paper summarizes the recent experience of one Army hospital and contributes data which may be helpful in reducing infant mortality by indicating channels for improvement.

The first requisite for the study of this problem is an estimate of the situation as it now exists. The careful and complete maintenance of the records is therefore essential. At the present time the number of stillbirths almost exactly equals the number of neonatal deaths. As has been emphasized by the Bureau of Medical Economic Research,[1] the neonatal rate may be artificially lowered merely by altering the definition of stillbirth. The combined neonatal and fetal death rate is, therefore, the only reliable criterion. Neither can be evaluated unless both are known. The situation is further complicated by variable standards for recording infants under 1,000 grams. We record all such births, but in Fig. 1 the "previable" group is inserted below the base line. We believe this system desirable so that our figures can be compared to those of others who use different criteria.

*Maternal mortality as used in this report means any death during pregnancy or the puerperium whether or not due to obstetric causes.

Of the last 10,000 deliveries at Brooke Army Hospital, 154 terminated in stillbirth. There were 152 neonatal deaths. A neonatal death is defined as any death occurring within one month after the date of birth. Since we deal with a controlled population, this necessitates only including late deaths

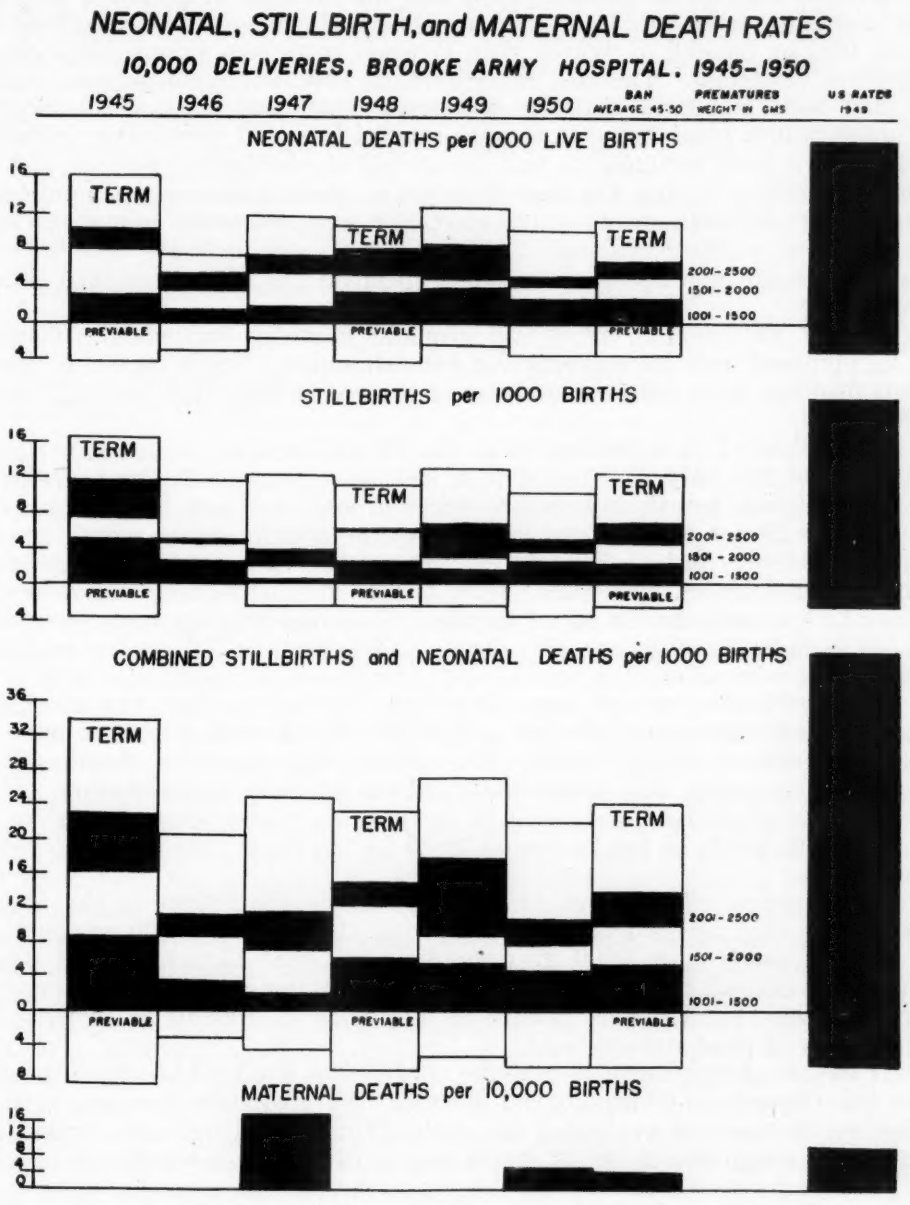

Fig. 1.

which occur on pediatric wards. The neonatal death rate is therefore 1.5 per cent, stillbirth rate 1.5 per cent, and the combined neonatal and fetal rate is 3 per cent. If the previable group under 1,000 grams is excluded, stillbirth and neonatal rates both drop to 1.2 per cent and the combined rate to 2.4 per cent. These figures are comparable to those of other teaching institutions

and are slightly over half as high as the average United States figures. A 50 per cent reduction in both stillbirth and neonatal rates for the country as a whole can, therefore, be anticipated as obstetrical standards and practice generally approach those of teaching institutions.

Without change in physical facilities, fluctuations in stillbirth and neonatal mortality rates can be related to personnel changes. Our highest rate was in 1945 at the end of World War II when there was a continuous change of medical personnel. The best rates were in 1946 when the personnel situation had been stabilized and the obstetrical staff was composed of mature and outstanding specialists. Although several hundred physicians, including interns, have been assigned to the Obstetrical-Gynecological Service and the Pediatric Service during the past four years, there has been no appreciable variation of stillbirth or neonatal mortality rate since the inauguration of the residency training program. This makes it seem probable that the most important factor is adequate direction of departments where standard policies are enforced.

Further reduction of fetal and neonatal mortality in teaching hospitals can be obtained only by methods not yet delineated. For a logical approach to this problem more detailed analyses of present current fetal mortality rates are required.

From Table I it is evident that the 92 per cent of births occurring at term account for only 33.6 per cent of the total fetal loss. Birth occurring after the eighth month but before term in only 6.7 per cent of patients accounts for 29 per cent of fetal loss. Births before the eighth month account for only 1.43 per cent of the total births but represent 37.1 per cent of the disappointed mothers. The total fetal loss is divided equally between stillbirths and neonatal deaths in all groups. Since the fatality rates vary from 89.2 per cent for infants born alive under 1,000 grams to 0.47 per cent for full-term infants born alive, it is obvious that the prevention of prematurity is the key to the reduction of this huge fetal loss. During the last two months of pregnancy the fetus gains over 100 grams a week. A week may thus mean the difference between life or death. The obstetrician (knowing that he rarely loses a mother) may now make the child his primary consideration. If by such exercise of medical judgment he is able to prolong pregnancy after the twenty-eighth week, he has increased by 25 to 50 per cent the infant's chances for survival.

In our series, 57 per cent of neonatal deaths took place in the first 24 hours. The rate varies from 76 per cent of those under 1,000 grams to 35 per cent of those over 2,000 grams. An additional 15 per cent of deaths occur in the second 24 hours. Between 80 and 90 per cent of deaths occur in the first week of life. This illustrates why it is so difficult to increase the survival rate of premature infants.

At Brooke Army Hospital periodic conferences are held at which the data from the Obstetrical-Gynecological Service, the Pediatric Service, and the Pathology Service are evaluated for each stillbirth and neonatal death. Although the assignable cause of death may still remain a matter of opinion, this practice is more reliable than the evaluation of cold records.

From the figures in Table I it is apparent that an infant's chances for survival are geometrically proportional to his weight. Only 34 percent of stillbirths and neonatal deaths occur in full-term infants. Primary disease of the fetus responsible for death is discoverable in less than 25 per cent of premature infants (Table II). Over 98 per cent of the remaining three-fourths would probably survive if carried to term, therefore, stillbirth and neonatal mortality would be reduced at least 49 per cent by the prevention of premature birth. The number of deaths not due to primary fetal disease is directly proportional to weight.

TABLE I. MORTALITY ACCORDING TO WEIGHT IN GRAMS AT BIRTH—10,000 BIRTHS

	WEIGHT IN GRAMS					
	UNDER 1,000	1,001-1,500	1,501-2,000	2,001-2,500	TERM	TOTAL
No. of infants	65	78	167	503	9,236	10,049
Percentage of births	0.65	0.78	1.7	5	92	100
No. stillborn	28	22	23	21	60	154
No. born alive	37	56	144	482	9,176	9,895
No. neonatal deaths	33	30	24	22	43	152
Total loss	61	52	47	43	103	306
Percentage of stillbirths	18.2	14.2	14.9	13.6	38.9	100
Percentage of neonatal deaths	21.6	19.2	15.8	15.2	28.2	100
Percentage of total loss	19.7	17	15.3	14	33.6	100
Premature Mortality Rates According to Weight in Grams at Birth.—						
Percentage of prematures	8.0	10.0	21.0	62.0		
Percentage stillborn	43.0	28.2	13.8	4.2		
Percentage born alive	57.0	71.8	86.2	95.8		
Premature mortality rates	89.2	53.6	16.7	4.6		
Percentage of total lost	93.8	66.7	28.1	8.6		
Mortality Rates for Term Infants.—						
Percentage stillborn					0.65	
Percentage neonatal deaths					0.47	
Percentage of total lost					1.1	

Frequency of Certain Conditions Associated With Stillbirths (Table II).—The majority of stillbirths are directly related to maternal complications. Of 154 stillborn infants, 72, or almost half, were associated with anoxia from abruptio placentae, placenta previa, cord complications, or placental insufficiency. Sixteen infants, or 10.4 per cent, had trauma, usually with intracranial hemorrhage, sufficient to explain death. In 25 instances, or 16.2 per cent, stillbirth was due to either congenital anomaly, or erythroblastosis. Maternal infection was responsible for eight, or 5.2 per cent of stillbirths. Five, or 3.2 per cent, of stillbirths were associated with maternal toxemia. In 26 cases, or 16.8 per cent, neither maternal nor fetal factors sufficient to explain fetal death could be discovered.

Causes of Neonatal Death. Primary or Secondary to Maternal Complications (Table II).—In contrast to stillbirths, the majority of neonatal deaths are traceable to fetal factors. Of the 152 neonatal deaths in this series, 16, or 10.5 per cent, were due to anoxia from abruptio placentae, placenta previa, or cord complications. These causes of anoxia are more likely to result in stillbirth than neonatal death. There were 135 cases of premature separation of the placenta in this series. From these 135 cases there were 30 stillbirths and 9 neonatal deaths. The combined mortality was 28.8 per cent. Placenta previa occurred in 38 instances, with 7 stillbirths and 5 neonatal deaths resulting. This is a combined mortality of 31.7 per cent. The majority of these infants were previable or premature, which accounts for the high mortality. Interference with circulation in the cord ordinarily results in stillbirth, rather than neonatal death. In this series there were 63 mothers with severe cardiovascular disease and 30 with severe pulmonary disease, with no fetal mortality, although these conditions often cause fetal anoxia.

Twenty-nine neonatal deaths, or 19 per cent, were due to trauma, usually intracranial hemorrhage. When intracranial hemorrhage is the cause of death, the infant usually survives for at least a few hours. As a result the ratio between stillbirths and neonatal deaths due to trauma is one to two. On many occasions intracranial hemorrhage is found to have been the primary cause of death at autopsy when delivery was neither complicated nor precipitate. The cause of intracranial hemorrhage in such instances is obscure. This is especially true of babies delivered by cesarean section.

In the last 10,000 deliveries, there have been 141 cesarean sections with 12 neonatal deaths. This is a section incidence of 1.4 per cent with a fetal mortality of 9.2 per cent. Thus, 1.4 per cent of the deliveries account for 8 per cent of neonatal deaths, or 4 per cent of the total fetal loss. The combined fetal mortality rate from cesarean section is therefore three times that from vaginal delivery (3.08 per cent). The average weight of these infants, however, was 2,540 grams and only two were below 2,000 grams. The combined rate for the vaginal route in infants over 2,000 grams is only 1.1 per cent so the fetal mortality rate for cesarean section is actually eight times as high as for vaginal delivery. Cesarean section remains the procedure of choice for many maternal complications, but should rarely be used in the primary interest of the fetus. When so used the result is too often tragic.

TABLE II. FREQUENCY OF CERTAIN CONDITIONS ASSOCIATED WITH STILLBIRTHS (AUTOPSY RATE 87 PER CENT)

	WEIGHT IN GRAMS							
	UNDER 1,000	1,001-1,500	1,501-2,000	2,001-2,500	TERM	TOTAL	% OF DEATHS	RATE PER THOUSAND
Anoxia							46.7	7.2
Abruptio	3	6	10	5	6	30		
Placenta and cord	4	4	3	5	19	35		
Previa		1		1	5	7		
Trauma	2	3	1	1	9	16	10.4	1.6
Congenital anomalies	5	1	5	3	5	19	12.3	1.9
Maternal infection	1	2			5	8	5.2	0.79
Diabetes					2	2		
erythroblastosis	1	1		1	3	6	5.2	0.79
Maternal toxemia		2	1	1	1	5	3.2	0.5–
Prematurity or unknown	12	2	3	4	5	26	16.8	2.6–
Total	28	22	23	21	60	154	100	15.3
CAUSES OF NEONATAL DEATH (AUTOPSY RATE 88 PER CENT)								
Anoxia							10.5	1.6
Abruptio	2	7				9		
Placenta and cord			1		1	2		
Previa	2			1	2	5		
Trauma	6	6	4	5	8	29	19.1	2.9
Congenital anomalies	2	2	6	7	14	31	20.4	3.1
Infant infection	1	1	2	1	4	9	5.9	0.9–
Diabetes, hemorrhagic disease, erythroblastosis	1	1	2	3	9	16	10.5	1.6
Pulmonary disease	1	5	7	5	4	22	14.5	2.2
Prematurity or unknown	18	7	2		2	29	19.1	2.9
Total	33	29	24	22	44	152	100	15.1

In our experience breech delivery has not been associated with increased fetal mortality. There were 322 breech deliveries in this series, an incidence of 3.2 per cent. There were seven stillbirths and five neonatal deaths, or a combined mortality of 3.7 per cent. However, when the weight of the infants is taken into consideration, mortality from breech delivery is no higher than that noted in vertex presentation.

It is often stated that the prognosis of premature twins is better than that of ordinary prematures. We find the mortality is directly correlated to weight, whether in multiple or single birth.

In 31 instances, or 20.4 per cent, major congenital anomalies, either obvious or discovered at autopsy, explained death. In the past, congenital anomalies were considered due to immutable causes. With the discovery that

maternal rubella in the first trimester of pregnancy produces severe anomalies (of the fetus) in at least 60 per cent of the cases and Dr. Warkany's classical experimental production of congenital anomalies by dietary deficiency, it becomes obvious that we can no longer assume a passive attitude toward congenital anomalies.[2] The private practitioner who has an intimate knowledge of the prenatal course of his patients is in the best position to discover other causes for congenital anomalies. Experimental embryologists, such as Willis,[3] can explain how most anomalies develop but not why. Admittedly in some instances the cause is an inherited defect. We have an example of a family in which hydrocephalus is sex linked, being transmitted through females to males. Even inherited defects are probably not completely beyond eventual control. Genotypes and phenotypes having been established, expressivity and penetrance are still variable and incomplete. Many congenital anomalies can be corrected by modern surgical intervention.

TABLE III

Neonatal Deaths From Congenital Anomalies.—	
Congenital heart disease	12
Intestinal obstruction	5
Multiple congenital anomalies	5
Genitourinary anomalies	4
Hydrocephalus	3
Diaphragmatic hernia	1
Meningocele	1
Stillbirths.—	
Anencephaly	7
Hydrocephalus	7
Congenital heart disease	3
Diaphragmatic hernia	1
Multiple congenital anomalies	1
Deaths of Older Children From Congenital Anomalies After Neonatal Period (1945-1950).—	
Congenital heart disease	16
Gastrointestinal tract anomalies, including pancreatic fibrosis	7
Hydrocephalus	4
Hydronephrosis	2
Congenital leucemia	1

These late deaths from congenital anomalies accounted for 23 per cent of the 130 pediatric deaths at Brooke Army Hospital from 1945 to 1950.

Although there were 96 cases of maternal syphilis in this series, only one death of a fetus resulted. Since the introduction of antibiotics, infection, other than epidemic diarrhea of the newborn, has become a rare cause of neonatal death. We have been fortunate in having no "nursery epidemic." In addition to the case of congenital syphilis, 8 infants in this group died from infection:

Septicemia, *B. coli*	4
Meningitis, *B. coli*	1
Pneumonia	1
Diarrhea	1
Peritonitis	1

In our small series of 11 cases of maternal diabetes, 2 infants were stillborn and 3 died after birth, a neonatal mortality of 27.2 per cent, and a combined mortality of 45.4 per cent.

If hemorrhagic disease of the newborn occurs, it is extremely rare. One death in this series was ascribed to this cause. However, all newborn infants in this series were given vitamin K.

Sensitization of the mother to an Rh factor occurs about once in each 200 deliveries. The development of erythroblastosis of the fetus which results from this sensitization accounts for less than 10 per cent of neonatal deaths. A tabulation of the problems of Rh sensitization in this series is as follows:

10,049 Mothers
1,300 Rh negative (13 per cent)
81 mothers either had or developed anti-Rh agglutinins (0.8 per cent of all mothers or 6.2 per cent of Rh negative)
8 of the 81 babies were Rh negative and normal (9.9 per cent)
10 babies were Rh positive and normal despite positive maternal anti-Rh agglutinins titer (12.3 per cent)
9 babies had no atypical agglutinins (negative Coombs) and were normal 11.1 per cent)
54 babies had erythroblastosis
12 had mild erythroblastosis with Coombs test less than 2 plus and did well without treatment (14.8 per cent of 81)
6 infants were stillborn because of erythroblastosis (7.4 per cent)
36 infants had clinical erythroblastosis with Coombs test over 2 plus (44.4 per cent of 81)

Treatment and results as follow:

	NO.	DIED	MORTALITY
Repeated transfusions as indicated	17	7	41%
Replacement transfusion	16	3	18%
ACTH (adrenocorticotropic hormone)	3	0	0

In 22 cases, or 14.5 per cent of neonatal deaths, the cause of death was hyaline atelectasis. In Dr. Potter's[4] series 57 per cent of the neonatal deaths were attributed to the development of this condition. This pulmonary disease seems to be becoming more common, but, to date, its etiology remains obscure. It may be related to our methods of resuscitation. It is especially common after cesarean section and in infants born of diabetic mothers. Only 10 per cent of the cases occur in full-term infants. It is never found in stillborn infants and rarely occur twice in the same family, although we have had one such instance.

Toxemia of pregnancy occurred in 425 (4.23 per cent) of the mothers in this series (Table IV).

TABLE IV

TOXEMIAS	STILLBIRTHS			NEONATAL DEATHS		FETAL LOSS
	NUMBER	PREMATURE	TERM	PREMATURE	TERM	
Hypertension (with and without superimposed acute toxemia)	18	0	0	0	0	
Pre-eclampsia	320	6	3	1		3.1 %
Eclampsia	56	0	1	1	0	3.6 %
Acute nephritis	1	0	0	0	0	
Total	395	6	4	2	0	3.04%

The two neonatal deaths associated with toxemia were due to anoxia caused by abruptio placentae. Although toxemia is an important maternal complication, it has little significance for the fetus. When the weight of the infant is taken into consideration, the mortality of infants delivered of toxemic mothers is no higher than of the controls. Toxemia may be said to be important to the fetus only to the degree that it increases the number of premature births, either spontaneously or from obstetrical interference.

In 29, or 19 per cent of neonatal deaths, chiefly of infants under 1,000 grams, no cause of death, either maternal or fetal, except prematurity, could be determined.

Summary

1. Maternal mortality rates are now so low that, for conservation of life, the fetus rather than the mother has become the primary concern of the obstetrician.

2. More deaths occur in the first month of life than during all other periods in the pediatric age group up to 15 years.

3. Of 150,000 fetal deaths each year, one-half are still births and one-half are neonatal deaths.

4. Ninety per cent of this fetal loss is attributed to prenatal and natal causes.

5. Pediatricians have requested and have been assigned the responsibility for the care of the newborn but they can function only as salvage officers whose results are limited by conditions already in effect.

6. Infants under 1,500 grams comprise only 1.4 per cent of deliveries, but 36.9 per cent of fetal and neonatal deaths are in this group. Over half of these infants die within 24 hours of delivery. Since the combined mortality rate in this weight group is 78 per cent, the only prospective method for reduction of fetal loss is the prevention of prematurity.

7. The infants who weigh between 1,500 and 2,500 grams comprise only 6.8 per cent of deliveries, but account for 29 per cent of the deaths. The combined stillbirth and neonatal mortality rate in this weight group has been reduced to 15 per cent and can probably be lowered further.

8. Ninety-three per cent of deliveries are at term but they account for only 33.6 per cent of fetal deaths.

9. Forty-seven per cent of stillbirths result from anoxia associated with premature separation of the placenta, placenta previa, or cord complications. An additional 10.4 per cent result from trauma. In 17.5 per cent stillbirth results from the fetal factors of congenital anomaly or erythroblastosis. In 16.8 per cent, the cause, other than prematurity alone, remains unknown.

10. In contrast to stillbirths, only 10.5 per cent of neonatal deaths are directly due to anoxia. About 19.1 per cent are due to trauma, chiefly intracranial hemorrhage discovered at autopsy. The remainder of neonatal deaths are explainable by congenital anomalies (20.4 per cent), infection (5.9 per cent), erythroblastosis or maternal diabetes (10.5 per cent), hyaline atelectasis (14.5 per cent), and prematurity or unknown (19.1 per cent).

11. In infants over 2,000 grams delivered by cesarean section the mortality rate is eight times that for those delivered by the vaginal route, and we are convinced that cesarean section should rarely be done in the primary interest of the fetus.

12. Toxemia of pregnancy is related to fetal and neonatal mortality only to the degree that it increases the absolute number of premature deliveries.

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FEMINIZING OVARIAN TUMORS AND PREGNANCY

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STERILITY is expected theoretically in the presence of feminizing ovarian tumors. They produce hyperestrinism that inhibits the pituitary and secondarily the remaining normal ovarian tissue. As a result, they are seldom seen among pregnant women. Coexistence of granulosa-cell tumors or luteomas and pregnancy has been observed experimentally among mice, but only when they were small.[13] A summary is presented of patients with known relation between tumor and pregnancy. The study shows that these neoplasms may produce serious complications during pregnancy or preclude pregnancy.

Patients

Case reports of 1,193 women with theca- (263 cases) or granulosa-cell (930 cases) tumors were collected from previous communications and by Diddle.[5] Data were cross indexed to eliminate duplications from various clinics. There were 37 instances, including 2 of our own, where there were sufficient data to evaluate the relation of these neoplasms to pregnancy. They form the basis of the discussion. The age was known for 29 of these women. More than one in 7 were in the second decade of life, over one-third in the third decade, while the others were in the fourth and fifth decades. Parity was known for 25 of the women. Two out of 5 were nulligravidas or nulliparas, while the remainder were either gravid or had previously been gravid.

Diagnosis

A correct diagnosis was never made preoperatively among women with feminizing ovarian tumors coexistent with pregnancy and seldom in those with abortive tendencies or with sterility. On the contrary, the diagnosis was usually suspected by gross examination of the neoplasm at the operating table or at postmortem examination.

Presentation of Clinical Data

Both the patients with theca- and granulosa-cell neoplasms were divided into three categories for purposes of discussion (Tables I and II), according to the relation of the symptoms and signs to pregnancy. One, the tumor was found during pregnancy or a few days post partum. Two, abortive tendencies antedated a correct diagnosis, and three, sterility preceded surgical intervention, which in turn was followed by pregnancy. In the last instance one or more other symptoms were present one-half to five years and included amenorrhea, metromenorrhagia, amenorrhea alternating with metromenorrhagia, or tumor.

Incidentally, 3 of the women with thecomas gave virilism as their chief complaint for intervals of one-half to 16 years.

TABLE I. THECA-CELL TUMORS

AUTHORS	AGE OF PATIENT* BY DECADE	PARITY	REMARKS
		Pregnant	
Diddle and O'Connor	4	Parous	Normal pregnancy
Dougherty and Lund	2	1	Died post partum of intraperitoneal hemorrhage
Patton and Patton	4	?	Criminal abortion in third month
Sternberg and Gaskill	2	1	Died post partum of intraperitoneal hemorrhage
Stout	2	Gravida i	Aborted 4 months after tumor removed
		Had abortive tendencies	
Falls, Ragins, and Goldenberg	4	?	Aborted in second month
Pali	4	Parous	Aborted in first trimester
		Antecedent sterility	
Dockerty	3	?	Later had 3 pregnancies

*Six of the patients were treated by either unilateral salpingo-oophorectomy or oophorectomy and the seventh and eighth were given antishock treatment.

Clinical Data

Thecomas were found among 8 of the 37 women. They were usually the size noted in our case report. None showed evidence of malignancy. Tumor and pregnancy were coexistent in 5 women. Two of these patients went into shock and died immediately post partum,[8, 35] each after giving birth to a normal infant. Autopsy examination showed massive intra-abdominal hemorrhage from rupture and torsion of the tumor. The third woman,[25] who had virilism for 16 years, had a criminal abortion in the third month the year the neoplasm was found. One could only theorize as to the outcome of this pregnancy if it had been allowed to progress normally. The fourth patient (the authors') had a known abdominal mass for 5 years. It was removed in the fourth month of gestation without disturbing the pregnancy. The fifth woman[36] conceived about the time the virilism appeared. She gave birth to a premature infant at the seventh month of pregnancy, or four months after the tumor was removed. Masculinizing signs did not disappear until four months post partum. It is unlikely that the premature birth had any relation to the neoplasm.

Two other women had abortive tendencies before a diagnosis was made. One patient[24] had a spontaneous abortion at the onset of the masculinization. In this instance, the growth possibly predisposed to the fetal loss. The other woman[9] aborted at the end of the second month of pregnancy. It is conceivable that this tumor also caused abortion through some endocrinologic disturbances.

An eighth woman, previously sterile, had three normal pregnancies after removal of a thecoma.[6]

In summary, three out of eight patients successfully carried their pregnancies to term with the thecoma present, but two of these died post partum of intraperitoneal hemorrhage. One in eight conceived after removal of the neoplasm; half aborted either before or after surgical treatment.

One-half of the women were well one-half to five years later, one-fourth died, and the remaining fourth were lost.

Granulosa-cell tumors were found among 29 of the 37 women studied.

TABLE II. GRANULOSA-CELL TUMORS

AUTHORS	AGE OF PATIENT* BY DECADE	PARITY	REMARKS
		Pregnant	
Bolli	3	?	Died post partum of intraperitoneal hemorrhage
Diddle and O'Connor	3	Gravida i	Found tumor post partum
Folsome	?	?	
Gerundo	?	?	Went to term
Greene	3	Parous	Died of metastases in second trimester
Greenhill	?	?	Found tumor postpartum
Henderson	4	Parous	Incidental finding at time of therapeutic abortion
Kusada	?	?	
Mitra	2	Gravida i	Tumor removed at fifth month, aborted at sixth month; later had normal gestation
Slamova	?	?	Tumor removed in second trimester; went to term
Spencer and Hollenbeck	4	Parous	Miscarried at 7 months
Strother	?	Gravida i	Ascites. Tumor removed. Went to term. Later conceived again
		Had Abortive Tendencies	
Meigs	5	Nonparous	Had 10 abortions
Powell and Black	3	?	Many abortions; normal pregnancy after tumor removed
Robinson	3	?	Previous abortion
Schultze	4	?	Abortion followed by amenorrhea for 9 years; had ascites
Spitz	4	Parous	Last pregnancy ended in an abortion and followed by 13 years' sterility
		Antecedent Sterility	
Ayre and Foote	4	?	Amenorrhea 5 years; conceived 2 months postoperatively
Countiss	4	0	Amenorrhea and episodes of bleeding for one year; conceived within a year postoperatively
Dockerty and MacCarty	4	0	Irregular bleeding 4 years; conceived fifth year postoperatively
French	4	Parous	Sterile 3.5 years; conceived within year postoperatively
Friesen	4	Parous	Amenorrhea 4 years; conceived postoperatively in 2 years
Hodgson, Dockerty, and Mussey	?	0	Conceived later; went to term
	?	0	Conceived later
Klaften	3	?	Amenorrhea 1 year; pregnancy 4 years postoperatively. Known recurrence 7 years postoperatively
Rhoads	5	?	Amenorrhea alternating with bleeding for 8 years; conceived 3 months postoperatively
Robinson	4	Parous	Tumor for 6 months; conceived 8 months postoperatively. Died later of recurrence
Schulze	3	0	Sterile 5 years; normal birth 2 years after tumor removed
Peralta Ramos	3	?	Conceived after second laparotomy for recurrence and had 2 babies thereafter

*Tweny-one women treated by either unilateral salpingo-oophorectomy or oophorectomy; one each by bilateral oophorectomy, and bilateral salpingo-oophorectomy and subtotal hysterectomy, one received antishock treatment, for five others no data available.

They proved to be malignant in 5 instances; the others were benign. Their size ranged from microscopic to near that noted in our patient.

Pregnancy was coexistent with the tumor among 12 women. One of the patients developed acute abdominal pain that was masked by labor, went into shock immediately post partum and died.[3] Postmortem examination showed intraperitoneal hemorrhage from rupture of the neoplasm. A second patient[37] noted rapid abdominal enlargement early in pregnancy. Part of the increase in size was found to be due to ascites. A laparotomy was done and the neoplasm removed. The pregnancy went to term. Two years later a second gestation ended spontaneously at the sixth month after premature rupture of the membranes. In a third,[32] fourth,[22] and fifth[14] instance the growth was apparently large enough to preclude vaginal delivery for removal was elected during pregnancy. One of these patients[22] aborted 3 to 4 weeks postoperatively at 6 months, later conceived again, and went to term. The neoplasm was found incidentally at the time a therapeutic abortion was done for a sixth woman.[17] The seventh woman had a premature infant born at the seventh month of gestation.[33] The eighth and ninth patients each gave birth to a normal baby. Immediately post partum their tumors were found. In one instance, the tumor was removed.[16] In the other, treatment was deferred by the patient. Subsequently, this woman had frequent uterine bleeding, eventually had an oophorectomy, and later had another normal pregnancy. Data regarding the tenth[10] and eleventh[20] women were unavailable other than that they were pregnant when their tumors were discovered. The twelfth[15] patient had a laparotomy in the second trimester of pregnancy, and died two weeks postoperatively of metastases.

There were five women, each of whom had one to ten abortions before their tumors were found.[21, 27, 29, 31, 34] One of these patients had several consecutive miscarriages. She gave birth to a normal baby[27] after removal of the neoplasm. Another woman developed metastases months later.[31] Follow-up on the remaining four was unavailable.

There were 12 women with antecedent sterility. After surgical treatment, nine women conceived within two months to five years.[1, 4, 7, 11, 12, 19, 28, 29, 30] One of these women developed amenorrhea subsequent to the pregnancy and attributable to a recurrence in the opposite ovary.[19] Another one gave birth to a normal baby in the second year postoperatively and died of a recurrence two years post partum or about four years postoperatively.[29] The tenth woman had a recurrence within a year, was laparotomized a second time and subsequently had normal babies in the third and fourth years, respectively, after the first operation was performed.[26] The eleventh woman conceived and went to term while the twelfth aborted at the fourth month of pregnancy. The time interval between oophorectomy and conception was unknown in both instances.

In summary, nearly one-half of the 12 pregnant patients with tumor went to term, a fourth aborted, and the outcome for the remaining third was unknown. After removal of the neoplasm there were 16 pregnancies among 15 women, yielding 6 viable babies, 2 nonviable fetuses, and an unknown outcome for eight others.

Nearly one-fifth of the women died, or were still living after a recurrence of the tumor. Over one-half were well without recurrence a few months to 16 years postoperatively, and over one-fifth were lost.

Case Report

These case reports are the only two of their kind from two institutions where the combined obstetric experience exceeds 25,000 patients.

CASE 1.—(Reported through the courtesy of Drs. E. D. Plass and W. C. Keettel.) The patient, a gravida iv, para iii, 39 years old, had normal menses with the last bleeding beginning Feb. 5, 1940. She was seen at the University of Iowa, April 30, 1940, with a history of a known, movable, abdominal mass for five years. It appeared after her last pregnancy. There was no discomfort until two months previously following conception. Then the mass became prominent and its movement produced twinges of abdominal pain. On physical examination a firm tumor was palpated in the right lower quadrant of the abdomen above Poupart's ligament. It was tender, fixed, and about 8 cm. in diameter. In the midline there was another nontender soft mass arising out of the pelvis one-third of the way to the umbilicus. By pelvic examination the uterus was the size of a three months' pregnancy, displaced to the left, and represented the soft mass felt abdominally. Bulging into the right fornix was the firm tumor felt above Poupart's ligament. On May 6, 1940, a right salpingo-oophorectomy was done. The left ovary was normal in size. The right ovary was adherent to the bladder and the tip of the appendix and filled part of the vesicouterine pouch. The uterus was the size of a 3 to 3½ months' pregnancy. There was no evidence of metastases.

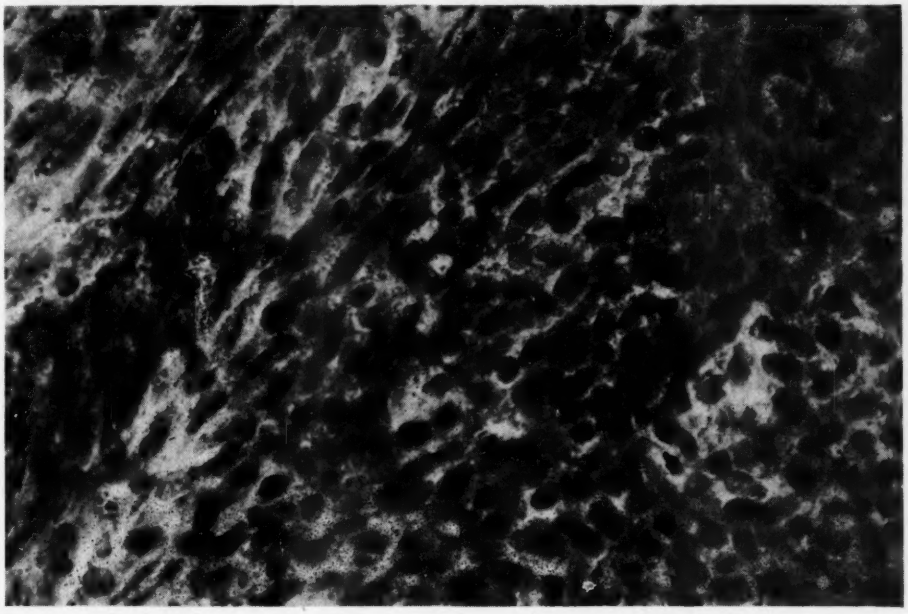

Fig. 1.—High-power photomicrograph of theca-cell tumor removed during pregnancy.

Gross Pathology.—The ovary measured 10 by 6 cm. It was irregular in contour, firm in consistency, and on bisection had a yellowish-white color. It was largely replaced by neoplasm. On one side of the ovary there was a small amount of normal-appearing ovarian tissue that contained a corpus luteum measuring 1.5 cm. in diameter.

Microscopic Pathology.—Part of the ovary was composed of interlacing bundles of spindle-shaped epitheloid cells intermingled with areas of degenerated tissue (Fig. 1). Fat tains showed intra- and extracellular fat. Sections from the grossly normal tissue revealed a small corpus luteum and ovarian stroma. A diagnosis of thecoma was made.

Follow-Up.—The patient was known to be well without recurrence of menstrual disturbance for nearly 18 months postoperatively.

Comment.—This is an example of a thecoma that induced no recognizable menstrual disturbance indicating its hormonal activity was either nil or its effect disguised by that of the normal ovary.

CASE 2.—(Hospital No. 86864.) A 22-year-old primigravida, after an uneventful prenatal period, gave birth to a normal, living, female infant weighing 7 pounds, 8 ounces at the

Oak Ridge Hospital, Oak Ridge, Tenn., on Oct. 3, 1945. The labor was uncomplicated and nine hours in duration. Nine days post partum a bimanual examination was done and a freely movable, solid, adnexal mass about 10 cm. in diameter was found lying to the right of the uterus and extending 4 cm. above the symphysis pubis. The patient was advised to have the growth removed, but she declined to follow the advice. Three months later she returned with the complaint of vaginal bleeding lasting 5 days and recurring every 14 days for the

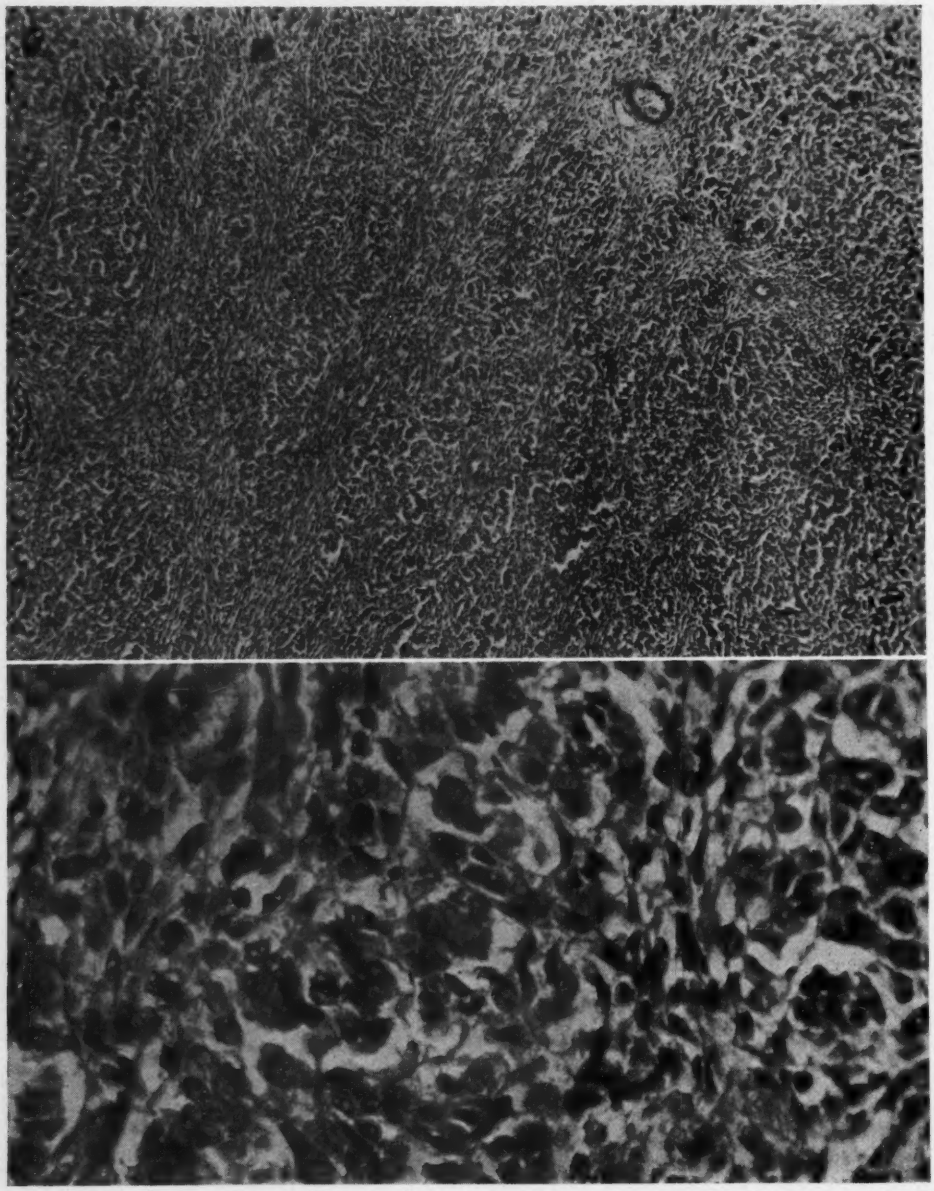

Fig. 2.—Low- and high-power photomicrographs of granulosa-cell tumor removed post partum.

last 2½ months. Pelvic examination showed the uterus to be of normal size. The right adnexal mass was the same size and consistency previously described. Feb. 12, 1946, or four months post partum, a diagnostic curettage and right salpingo-oophorectomy were done.

Gross Pathology.—The ovary was smooth, pink in color, and replaced by an encapsulated tumor measuring 10 by 8 by 5 cm. On bisection the tissue was yellow to grayish pink. The

other genital organs and viscera appeared to be normal. The curettings had a translucent appearance.

Microscopic Pathology.—Unfortunately, the histologic data were unavailable on the endometrial tissue. Multiple sections of the ovary showed a scant amount of ovarian stroma with extensive proliferation of moderate-sized granulosa cells arranged in tortuous columns and with a sarcomatoid pattern predominating. The nuclei of these cells were vesicular and the cytoplasm scanty in amount. In some areas there was necrosis with obliteration of cellular detail (Fig. 2). A diagnosis was made of a granulosa-cell tumor of the ovary.

Follow-Up.—Subsequently, this patient menstruated every 28 days up to June 3, 1946. She conceived again, had a normal prenatal course and gave birth to a normal infant on March 10, 1947. In August, 1950, or more than 4 years postoperatively, there was no evidence of recurrence and menstruation was regular and of normal quantity.

Comment.—Although hormonal studies were not done it is apparent that this tumor was not active enough to preclude pregnancy. To the contrary, the frequent bleeding post partum may have been due to the effect of the neoplasm for after its removal the menses thereafter were normal.

Comment

Amenorrhea seen with feminizing ovarian tumors is attributed to the continued increase in the estrogenic level. Only with its drop does bleeding occur (Henry[1]). In instances where pregnancy continued undisturbed it appears that the neoplasm produced little, if any, hormonal activity. Contrariwise, abortive tendencies suggest hormonal imbalance that might be attributed to the neoplasm. It may be significant that abortive tendencies were usually noted in the first trimester at the time developmental and endocrinologic disturbances in pregnancy are most likely to become recognizable. It is not surprising to see that some women were sterile before the tumor was removed but conceived after its removal. Theoretically, ovulation was precluded by the production of an excess of estrogens. A consideration of the 1,193 patients with feminizing tumors previously mentioned shows that these growths presumably precluded pregnancy often, because nulligravidity was seen in nearly one-third of the adult women with thecomas and over one-fifth of those with the granulosa-cell type where parity was known. The others had had one or more pregnancies. Unfortunately, the number married was unavailable. But, it was observed that 62 married women with granulosa-cell tumors were more often sterile than the average married woman in reproductive life.[18]

The histologic pattern found during pregnancy did not differ from that seen in nonpregnant patients. The neoplasms were either small or of moderate size. The largest were approximately the size of a two months gravid uterus.

Among three of the patients with thecomas there was enough hormonal activity to produce masculinizing signs. On the contrary, there was not enough to prevent the onset of pregnancy. This same sort of relationship was reviewed with arrhenoblastoma and pregnancy.[23] The masculinizing effect caused by a few thecomas lends physiologic evidence to substantiate Teilum's[38] opinion that some feminizing ovarian tumors are not far removed from male testicular tumors. The type of neoplasm depends along which line development occurred from the mesenchymal cell. Bali and Furth[2] observed experimentally that complex growths may arise in irradiated ovaries and contain both male and female elements.

Expressed in percentage, the theca-cell tumor was more often associated with abortive tendencies than was the granulosa-cell variety. However, since there were so few patients involved, this observation has an equivocal value.

This study revealed that a woman may have a feminizing ovarian tumor removed, bear children thereafter, and still have a fatal recurrence years

later. It also emphasized the hazard that may come to a parturient with a solid feminizing neoplasm large enough to undergo torsion. Since there is a paucity of framework in these growths and often a minimum of blood supply, necrosis, cyst formation, and hemorrhage are not uncommon.

Summary

The case histories of 37 women with feminizing ovarian tumors, 8 thecomas and 29 granulosa cell, were studied. Two were described by the writers and the other 35 were obtained from the recorded experience of others. The physiologic behavior of the neoplasms was considered in three groups in relation to their effect on pregnancy. In one, the tumor and pregnancy existed together, in another abortive tendencies antedated the diagnosis, and, in the third, the neoplasm apparently precluded conception through its hormonal activity. After its removal pregnancy occurred.

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MISTAKES IN INTERPRETATIONS OF INTRAEPITHELIAL CARCINOMA

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INTRAEPITHELIAL carcinoma of the uterine cervix has been a topic of renewed interest during recent decades. Following its introduction by Schottländer and Kermauner in 1908, the concept of surface cervical cancer was accorded little clinical attention until the epic studies of Schiller, published in 1928, presented histological evidence that cancer might exist and be detected in a preinvasive stage. More recent contributions, notably those of Pemberton and Smith, Stevenson and Scipiades, Te Linde and Galvin, Pund and Younge, etc., have revived consideration of the subject and have stimulated our search for cervical cancer in the noninvasive stage. As a result of this intensified quest, the microscopical appearance of the cervical epithelium has been subjected to increasing scrutiny, and minor degrees of departure from the normal have been recognized and identified by such terms as "basal-cell hyperactivity," "simple atypical epithelium," etc. Furthermore, these slight alterations in the cervical epithelium are viewed suspiciously by some as possible progenitors of "carcinoma in situ," thus reviving the earlier "rubric pattern" of Hinselman with its scaled gradations from normal cervical epithelium to true carcinoma.

The histological entity of intraepithelial carcinoma has been so generally accepted and the term has become so popular that one may fail to appreciate the fact that microscopical identification of intraepithelial carcinoma is an exacting task. At just what stage in its evolution can intraepithelial carcinoma be diagnosed with relative certainty? How can it be distinguished from the various benign abnormalities which may mimic it so closely and yet in themselves be entirely innocuous? These are problems which vex the discriminating pathologist.

We, of the Gynecological Pathology Laboratory at the Johns Hopkins Hospital, are quite aware of the difficulties that beset the correct microscopical diagnosis of intraepithelial carcinoma. That others experience these same difficulties is apparent from histological sections, forwarded to us from other laboratories, in which it is manifest that the diagnosis of intraepithelial carcinoma has been made on insufficient evidence and a patient has been subjected to an unnecessary operation. Because of this disturbing experience we felt it expedient to review our own cases in which the diagnosis has been made preoperatively but not confirmed by laparotomy.

Material

This review, covering the past nine years, presented us with the embarrassing conclusion that in twenty-five cases the histological examination of a removed cervix failed to confirm a diagnosis of intraepithelial carcinoma made on one or more preoperative cervical biopsies. Nevertheless we feel it is our duty to bring these errors to the attention of pathologists and gynecologists, for only careful study of these misinterpretations can crystallize our criteria for the correct diagnosis of this relatively new pathological entity. In a few of these patients there were other indications for major pelvic surgery but in the remainder a preoperative diagnosis of cervical carcinoma was the sole reason for total hysterectomy. The individual case histories as well as all pathological specimens of these twenty-five patients were reviewed and analyzed in an effort to disclose the source of error in each.

A study of the clinical factors of age, race, parity, the date of last pregnancy, the history of treated or untreated venereal disease, etc., was unrevealing, as were also the coexisting symptoms and the appearance and consistence of the cervix. The source of error in almost all of these twenty-five cases was the misinterpretation of the microscopical findings in the preoperative cervical biopsies. These deviations seem to fall within the three main categories discussed in the following paragraphs.

1. Removal of All the Carcinoma by Biopsy.—This group, comprising only two cases, is mentioned with some reluctance as such an explanation seems an attempt to justify a probable misinterpretation. However, the cervix in each of these two cases is described as possessing a small discrete ulcerative area, which was biopsied. The respective biopsy after very critical re-examination seems to justify the criteria for making the diagnosis of intraepithelial carcinoma, although multiple sections of the removed cervix presented no evidence of malignancy. The possibility of removing all the carcinomatous tissue in one small biopsy specimen seems tenable if we accept Wespi's suggestion that although carcinoma may become invasive in several different areas, originally there is a localized area *(Belag)* of carcinoma in the surface epithelium. Although we feel the above two cases are correctly catalogued we believe that such an occurrence is very infrequent. Fig. 1 illustrates such a specimen.

2. Technical Errors.—Under this caption are grouped the errors resulting from a failure to recognize cellular distortion incident to improper staining, or incorrect evaluation of the picture of massed overactive cells resulting from tangential cutting of the imbedded material. Insistence upon sufficient tissue for microscopical examination before passing judgment is a sine qua non. Even an adequate biopsy, however, properly imbedded and cut, may, if overstained, convey the false impression of hyperchromatosis of the epithelial cytoplasm or pyknosis of the nuclei and impart a generally ominous appearance to an essentially innocuous epithelium.

An unavoidable laboratory vagary in the preparation of tiny bits of tissue, as in cervical biopsies, is tangential sectioning. When this involves the basal portion of the surface epithelium, we are presented with a mass of unstratified, deeply stained cells with occasional nuclear mitoses which may be interpreted as representing the full vertical thickness of the surface epithelium and thereby present a picture simulating malignancy. Or if the tangential section occurs through one of the normal papillary projections of the surface epithelium, clumps of deeply stained basal cells surrounded on all sides by connective tissue may mimic stromal invasion.

Failure to appraise properly the artefacts of staining and misinterpretation of tangential sectioning of surface epithelium accounted for diagnostic errors in six instances. Fig. 2 is illustrative of such a section.

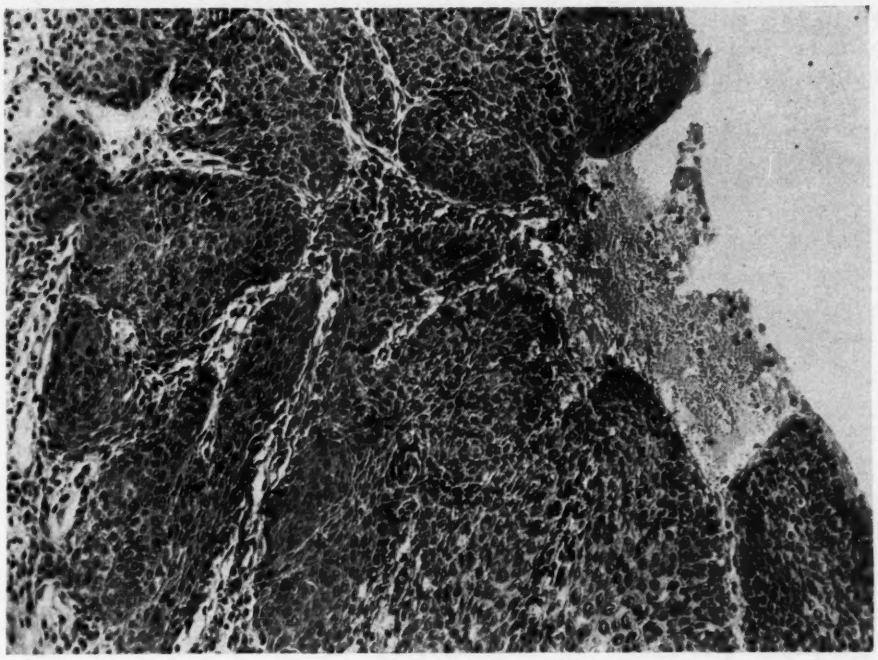

Fig. 1.

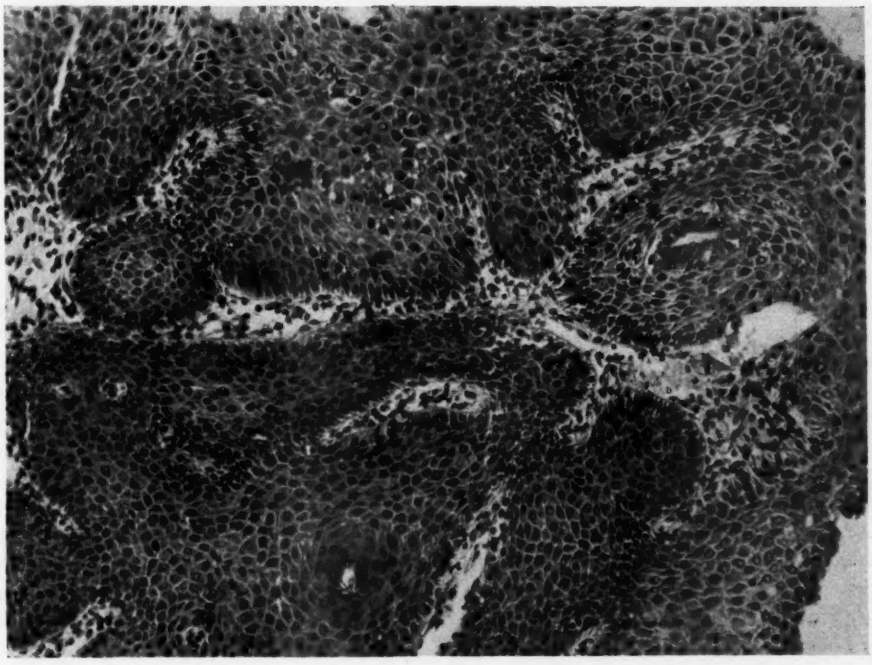

Fig. 2.

Fig. 1.—Typical early carcinoma found in preoperative biopsy. Serial section of the cervix removed at subsequent laparotomy showed no evidence of cancer.

Fig. 2.—Many pegs and sheets of cells can be seen deep in the stroma. Note, however, the well-differentiated cells, the mosaic pattern, and the unbroken basement membrane.

3. Misinterpretation of Biopsy.—The majority of our cases must be assigned to this category which comprises in particular those errors incident to an incorrect evaluation of "basal-cell hyperactivity" or to a misinterpretation of "epidermization."

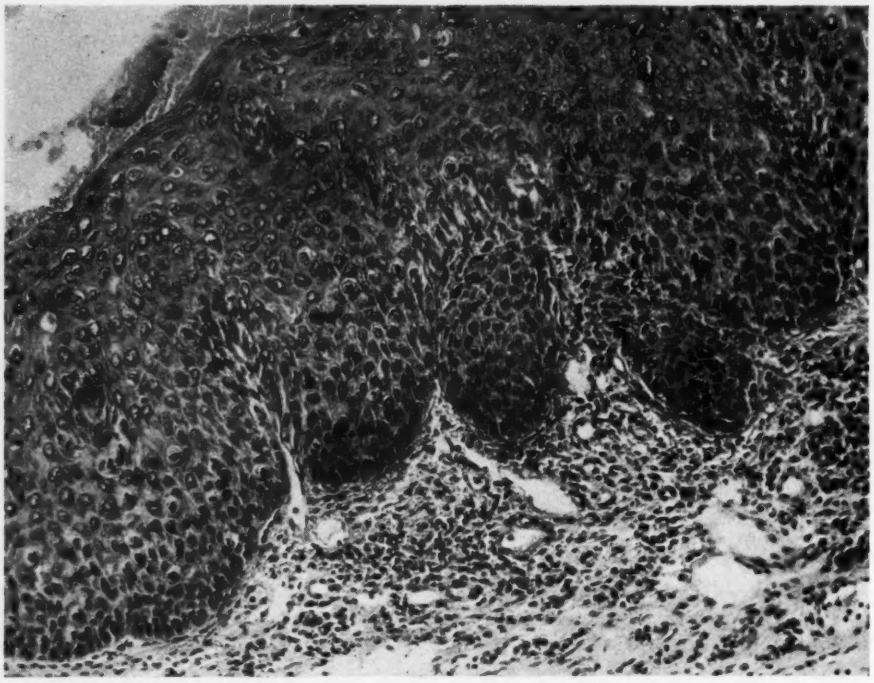

Fig. 3.—Moderate degrees of basal-cell hyperactivity are apparent. Note that some stratification of superficial layers is present. Leucocytic infiltration and vacuolization, probably an inflammatory response, impart an ominous appearance.

The microscopic picture as well as the significance of basal-cell hyperactivity has already been described adequately in earlier communications. Although we have encountered some evidence that it may be a progenitor of intraepithelial carcinoma, the majority of our cases when properly evaluated and observed over a period of months and years have shown a regression to normalcy. We are particularly impressed with the role that pregnancy and acute pelvic inflammatory disease might play in the production of this microscopic picture and feel that in the presence of either of these conditions one should be very hesitant to undertake any definite diagnosis or undertake any definitive therapy. Our own experience has taught us that we should regard this microscopic picture of basal-cell hyperactivity with extreme suspicion but we should also be very careful to differentiate it from full-fledged intraepithelial carcinoma. Our present study disclosed that in the past we have been too indiscriminate in our interpretation of epithelial changes in fourteen instances and have been too rash in instituting therapy on the basis of minor epithelial alterations in the biopsy specimen. Figs. 3 and 4 are representative.

In the remaining seven cases of our study in which the diagnosis of intraepithelial carcinoma was made on the cervical biopsy and subsequently proved incorrect, review of the sections indicates that the error was due to a misinterpretation of "epidermization." Robert Meyer has presented us with a

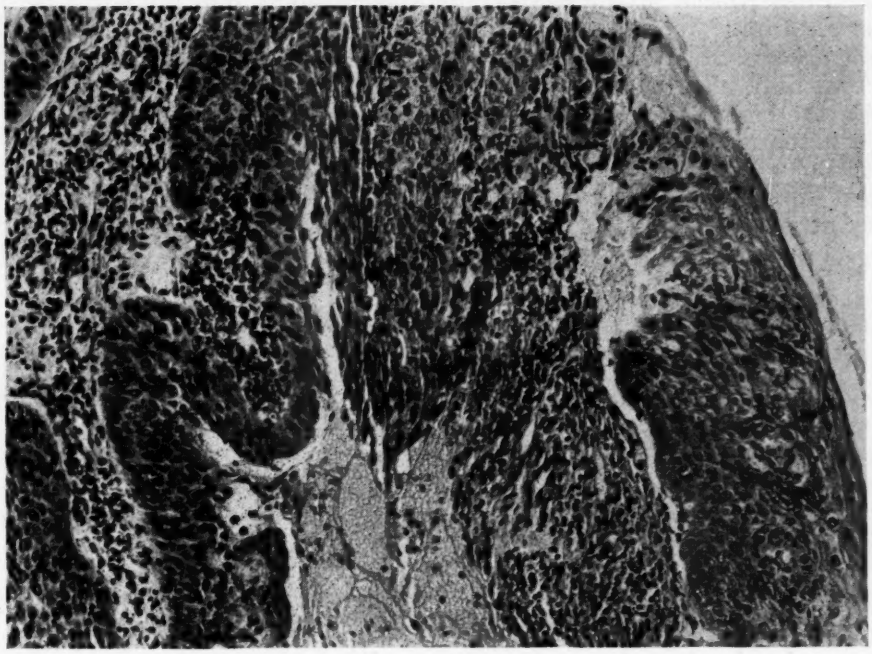

Fig. 4.—Basal activity on right. Epidermization on the left with rather immature squamous cells replacing the usual columnar epithelium. Imperfect stratification is often found at the squamocolumnar junction.

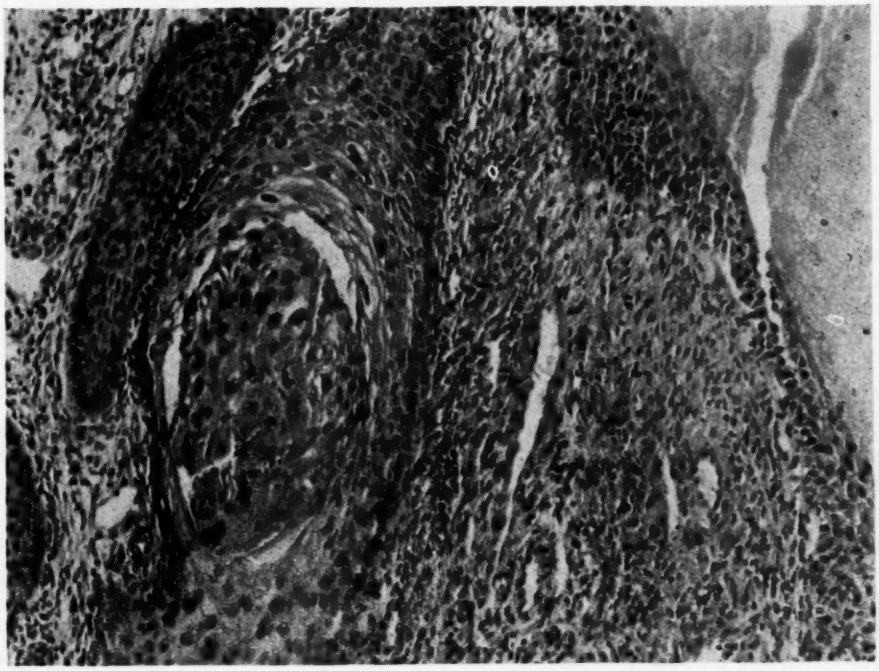

Fig. 5.—Obvious squamous metaplasia showing degenerative changes in cell nests. These should not be mistaken for the nuclear changes of malignancy.

detailed description of the genesis, the development, and the adult picture of epidermization. While demonstrating that in all its characteristics it is a benign process, Meyer also indicated that in some respects it mimics carcinoma and that only close attention to cytological details will enable one to differentiate the benign from the malignant. While in the great majority of cases this differentiation presents no problem to the experienced pathologist, there are instances where one is hard pressed to declare whether a microscopic picture represents cancer or epidermization. In seven instances the removed cervix attested that we had failed to distinguish between benign epidermization and intraepithelial carcinoma. Fig. 5 is from such a case.

Comment

The review of these twenty-five cases, in twenty-three of which we have made incorrect diagnosis of intraepithelial carcinoma, is somewhat humiliating. However, since these are errors of judgment rather than errors of ignorance or neglect, we do not feel too culpable. To us this study is a resolute reminder of the snares to which the overzealous and not too critical pathologist is a prey and it forcefully re-emphasizes that there is no substitute for experience in the interpretation of cervical biopsies.

It has become increasingly apparent that the cervical epithelium, particularly that at the squamocolumnar junction, can no longer be regarded as static, but that it is highly susceptible to various alterations although the factors responsible for these epithelial modifications are poorly understood. Schiller, Meyer, and Hinselman have emphasized the malignant characteristics inherent in some of these cellular alterations, and we agree that increasing loss of stratification in the normal mosaic pattern of cervical epithelium with replacement of these cells by less mature cells must be regarded with a high degree of suspicion. However, we insist that in our present state of knowledge we should withhold a diagnosis of cancer until the entire thickness of the surface epithelium is replaced by cells possessing the characteristics of malignancy. In some cases it is true that the cellular alterations of "basal-cell hyperactivity" when left untreated have been observed to progress into true malignancy. Less emphasized is the fact that the majority of such cases when followed over a period of months or years revert to normal. In this regard we repeat our interest in the epithelial transformations, simulating malignancy, occasioned by the stimulus of pregnancy or acute local infections which apparently regress when the stimulus ceases or is eliminated. Doubtless there are other unknown stimuli capable of producing cellular unrest, which may or may not be transient. Since we have at present no means of determining in which cases this "cellular unrest" is a permanent alteration capable of developing into cancer, we must resort to patient observation.

The most important lesson that we have derived from this study is that a patient should never be treated for intraepithelial carcinoma until such a diagnosis can be made with certainty on the cervical biopsy. If the microscopic appearance of the biopsy does not fulfill all the criteria for surface cancer, then periodic biopsies alone should be advised until such a diagnosis can be made or eliminated. To be even more cautious, once the diagnosis seems likely on the basis of one or more cervical biopsies, sharp conization of the cervix may be carried out. Examination of this generous sample of tissue can nearly always settle the question. We have lately introduced this as an almost routine diagnostic procedure before definitive therapy is instituted and we have been more than gratified with our results. Our experience with smears on these borderline cases has not been very helpful.

In advising a prolonged period of observation of patients whose cervical biopsies arouse some suspicion of malignancy it must be emphasized that clinical and pathological studies indicate that preclinical cervical carcinoma or intraepithelial carcinoma progresses extremely slowly over a period of years and that observation of the patient until the diagnosis is established does not jeopardize her chance of cure. We feel that the finding of minor degrees of cellular hyperactivity in cervical biopsies is never an indication for radical therapeutic measures but rather an indication to keep the patient under close surveillance. Only by such measures will we eliminate unnecessary radical surgery.

Summary

1. Twenty-five cases in which a diagnosis of intraepithelial carcinoma was made by preoperative biopsy but not confirmed by laparotomy have been analyzed for their sources of error.

2. The most common mistake leading to premature unnecessary operation has been a misinterpretation of varying degrees of basal-cell hyperactivity for genuine carcinoma in situ.

3. Patients suspected of intraepithelial carcinoma should never be treated hastily and all cases should have repeat biopsy confirmation. Possible confusing and mimicking lesions should be ruled out where possible.

4. Where biopsies are repeatedly equivocal, sharp conization of the cervix is recommended as a valuable diagnostic adjunct.

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THE RELATIONSHIP OF PROLONGED LABOR TO FETAL MORTALITY

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GREAT strides have been made in recent years in the handling of major obstetrical problems. Chemotherapy and antibiotics have virtually eliminated puerperal sepsis. Readily available blood has reduced greatly the morbidity and mortality from hemorrhage, and careful prenatal observation and early treatment have lowered both the incidence and the mortality rate from eclampsia. The development of accurate methods of x-ray pelvimetry has made it possible to improve the treatment of dystocia due to pelvic contracture. Our ignorance of uterine physiology, however, has prevented similar improvement in the handling of dystocia associated with ineffectual labor. This ignorance is well illustrated by the variety of terms by which this complication is known. Regardless of whether we speak of uterine inertia, uterine atony, cervical dystocia, or prolonged labor, the underlying difficulties are now recognized to be due to dysrhythmic uterine contractions alone or combined with dilatory cervical progression.

Treatment has varied from watchful expectancy to operative interference and stimulation, often culminating in a combination of all three. Several reports from large teaching clinics have appeared in the last few years dealing chiefly with the treatment of uterine inertia with intravenous Pitocin or Pituitrin. The general policy of the Boston Lying-in Hospital concerning the use of pituitary extracts has recently been outlined.[1] However, with the exception of the work of Douglas and Stander,[2] there has been minimal recent investigation of the causes of fetal death associated with prolonged labor.

It seemed worth while, therefore, to review the records of the Boston Lying-in Hospital in this respect, and at the same time to attempt a correlation of autopsy findings with various clinical events. Such an investigation involved analysis of all premature and term infant autopsies, and these will be considered briefly. A discussion of the fetal mortality in cases of prolonged labor will then be undertaken.

Material

During the period from Jan. 1, 1931, when the Pathological Laboratory was established, to Dec. 31, 1950, a total of 83,763 term and premature deliveries, representing 85,945 births, occurred in the Boston Lying-in Hospital and Richardson House. There were 3,179 stillbirths and neonatal deaths, an over-all uncorrected fetal loss of 3.7 per cent of infants weighing over 1,000 grams.

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The fetal autopsy rate was relatively low, 38 per cent representing 1,233 autopsies. There were 735 term infants and 498 prematures. The clinical record together with the autopsy protocol was reviewed in each case.

Results

Fig. 1 shows the causes of infant death in these 1,233 autopsies for the 19-year period, arranged in a clinicopathologic classification. This method was adopted because it was felt that it more closely represented the actual etiology of death than would a purely pathological grouping. Asphyxia was actually the most common pathological finding, but in Fig. 1 asphyxia includes only those deaths in which there was no other obvious cause. For example, when asphyxia was associated with placental or uterine accidents or severe maternal disease, the death was classified under maternal factors. Similarly, deaths from prolapsed cord, malformations, intracranial hemorrhage, and infection all showed variable degrees of asphyxia pathologically.

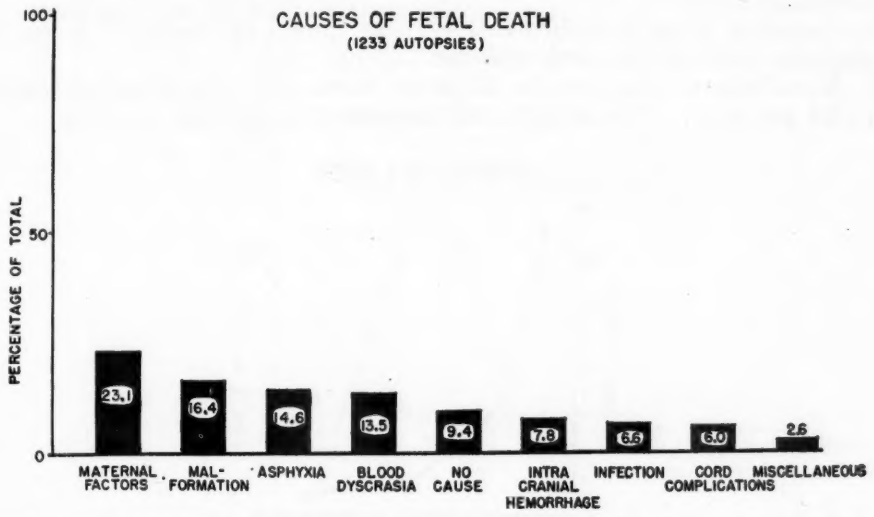

Fig. 1.—Causes of fetal death in 1,233 consecutive autopsies at the Boston Lying-in Hospital.

1. Maternal Factors.—This group accounted for 286 fetal deaths (23.1 per cent) and included principally placenta previa, abruptio placentae, uterine rupture, toxemia, diabetes, and intercurrent infection. Premature labor occurred in 76 per cent of these cases.

2. Congenital Malformation.—These accounted for 203 deaths (16.4 per cent) and included only those abnormalities incompatible with life.

3. Asphyxia.—There were 179 deaths (14.6 per cent) due to asphyxia. In many of these the predisposing factors were not clear, and, indeed, in 45 per cent it was impossible to ascribe death to any one cause. In 21 cases, however, tumultuous labor was present. Twelve infants were premature, and all 21 showed atelectasis and marked cerebral edema and congestion.

Difficult delivery caused asphyxia in 18 infants, 8 of these occurring in patients having contracted pelves. Major problems included prolonged pressure of the fetal head against the perineum, especially in prematures, forceful suprafundic pressure to effect delivery, or difficult mid- and high forceps and difficult breech extraction.

Excessive analgesia and anesthesia could be definitely incriminated in 10 deaths, 4 of them premature babies.

The role of postmaturity in the susceptibility of infants to asphyxia was not considered because there is no satisfactory definition of postmaturity at the present time.

4. Blood Dyscrasia.—There were 166 infant deaths (13.5 per cent) in this group. Twelve apparently had hemorrhagic disease of the newborn and 134 were associated with Rh sensitization.

5. No Cause.—In 115 infants (9.4 per cent), 74 per cent of whom died before the onset of labor, no cause for death could be found. There were 29 neonatal deaths, all in prematures.

6. Intracranial Hemorrhage.—This accounted for 96 deaths (7.8 per cent), the majority associated with traumatic delivery. Twenty were breech extractions (10 through contracted pelves), and the remainder were vertex presentations, 11 being associated with contracted pelves and difficult high or midforceps. In 18 cases the only apparent factor was a tumultuous period of labor.

7. Infection.—Infection was responsible for 82 fetal deaths (6.6 per cent). The majority were due to pneumonia, usually associated with prolonged labor and chorioamnionitis.

8. Umbilical Cord Complications.—These caused 74 deaths (6.0 per cent). The majority were due to cord prolapse.

9. Miscellaneous Causes.—In 32 cases there were miscellaneous causes of death (2.6 per cent). There were only 3 cases of congenital syphilis.

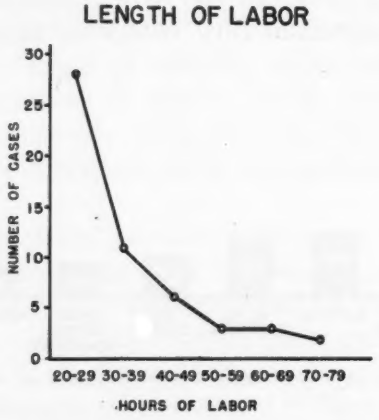

Fig. 2.—Length of labor in the 53 cases classified as prolonged. Seventy-five per cent of the labors were under 40 hours.

The Relation of Prolonged Labor to Fetal Mortality

For statistical purposes we have defined prolonged labor as 20 or more hours of true labor, the onset being based on progressive effacement and dilatation of the cervix.

The clinical records of 202 cases of prolonged labor were reviewed. All of these occurred since 1938, since prior to that time these cases were not indexed. Thirty-seven infants in this group died and were autopsied, a fetal mortality rate of 18.3 per cent. An additional 16 infants from prolonged labor cases were autopsied during the 1931 to 1937 period. In all, 53 infants who died during or following prolonged labor were autopsied.

Results

Age and Parity.—The age of the 53 mothers resembled the clinic average in that 80 per cent were 30 years of age or younger. Ninety-one per cent were

primigravidas, of whom 2 were "elderly." All multiparas had some degree of fetopelvic disproportion.

Weight.—There were few patients who varied widely from the average weight for their height-weight ratio and only 1 belonged to the "dystocia-dystrophy" type. Weight gain did not vary from the clinic average.

Length of Labor.—The variation in lengths of labor is shown in Fig. 2. It is evident that 75 per cent of the patients had total labors under 40 hours and 50 per cent had labors under 30 hours. The following factors were analyzed in their relation to the length of labor:

a. *Fetal size:* From Fig. 3 it is evident that the infant weights in general followed a normal distribution curve and there was only one premature in the series (an anencephalic). There were 12 infants weighing over 4,000 grams and 5 between 3,800 and 4,000 grams. There was definite evidence of fetopelvic disproportion in 14 of these 17 cases.

b. *Presentation:* There were 3 breech and 1 posterior face presentations in the series. The remainder were vertex presentations, including 13 occiput posterior, and 23 occiput transverse.

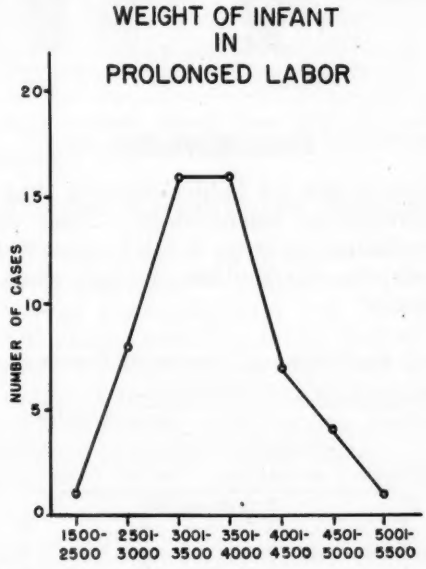

Fig. 3.—The weights of the infants in the prolonged labor series, showing a normal distribution curve.

c. *Character of labor:* Twenty patients had a prodromal period of irregular contractions and 40 had poor early contractions with slow progress from the onset of labor. Thirteen others also ceased labor, after having good contractions initially. Sixty-six per cent of the patients who ceased labor did so before 20 hours and with the cervix 50 to 75 per cent dilated.

d. *Induction of labor:* There were 4 patients who had artificial rupture of the membranes for various indications. All had a latent period of over 18 hours before the onset of labor. The cervix was "unfavorable" in all four.

e. *Analgesia:* The use of analgesic drugs apparently played a role in the retardation of 19 labors, usually because of large doses of medication given to patients whose lack of progress was not recognized. Only one patient received no medication.

f. Therapeutic procedures: Only 24 of the patients had diagnostic sterile pelvic examinations during labor. Rupture of membranes after labor had slowed or stopped was resorted to in 11 cases. Only about one-half the patients had x-ray pelvimetry. Approximately one-third were treated by sedation after progress slowed or stopped and only one-half of the patients received supportive intravenous fluids. Antibiotics were not used prior to 1947. In two-thirds of the cases, however, some type of pituitary extract was administered, but less than half were benefited by its use. The failure of pituitary extract occurred chiefly in the earlier cases when its appropriate use was poorly understood.

g. Type of delivery: Table I shows the type of delivery in each of the 53 cases. The decrease in cesarean section in the latter group demonstrates that abdominal delivery is now usually practiced before the infant's survival is jeopardized.

TABLE I. TYPE OF DELIVERY

	CESAREAN SECTION	HIGH FORCEPS	MID FORCEPS	LOW FORCEPS	SPONTANEOUS	BREECH VERSION	DESTRUCTIVE OPERATION
1931-1937	6	2	3	2	3	0	1
1938-1950	1	0	12	11	7	3	2
Totals	7	2	15	13	10	3	3

Fetal Mortality

Autopsy examination of the 53 babies showed that 42 presented signs of asphyxia and 10 had intracranial hemorrhage. There was 1 anencephalic monster. Thirty-four asphyxiated infants, 5 with intracranial hemorrhage, were stillborn. Table II shows the distribution of these cases according to the chief contributing cause of death.

TABLE II. CAUSES OF FETAL AND NEONATAL DEATH IN PROLONGED LABOR AND CONTRIBUTING CAUSES

	MAJOR CAUSES					
	ASPHYXIA			INTRACRANIAL HEMORRHAGE		
CONTRIBUTING CAUSES	STILLBORN	NEONATAL	TOTAL	STILLBORN	NEONATAL	TOTAL
Infection	20	6	26	–	–	0
Delivery technique	3	1	4	5	4	9
Sudden, rapid labor	3	0	3	–	–	0
Medication	1	1	2	–	–	0
Congenital defect	1	0	1	–	1	1
None	7	0	7	–	–	0
Totals	35	8	43	5	5	10

Among asphyxial deaths infection is the leading cause. In 19 of these 20 cases a chorioamnionitis was discovered, clearly demonstrating the relation of prolonged labor to amniotic-sac infection and fetal pneumonia. Only 3 of these patients, however, received antibiotics. Difficult delivery caused 4 deaths from asphyxia, 2 associated with shoulder dystocia and 2 with difficult forceps. Three further deaths were caused by violent contractions late in labor and 2 could be definitely ascribed to medication shortly before delivery. There were 7 stillborn infants in whom no direct contributing cause could be found, although intrapartum fever existed in 4 of these cases.

The deaths of nine of the 10 infants having intracranial hemorrhage were associated with traumatic delivery. Seven involved difficult forceps rotations and 2 difficult forceps extractions. Five were done at midstation and 2 were

classified as high. The other death from hemorrhage was that of an infant delivered spontaneously with craniotabes.

Fig. 4 compares the deaths from asphyxia and intracranial hemorrhage in the prolonged labor group and in the entire hospital series. It is evident that asphyxia was five times as common in the prolonged labor group; intracranial hemorrhage was only two and one-half times more common in this group.

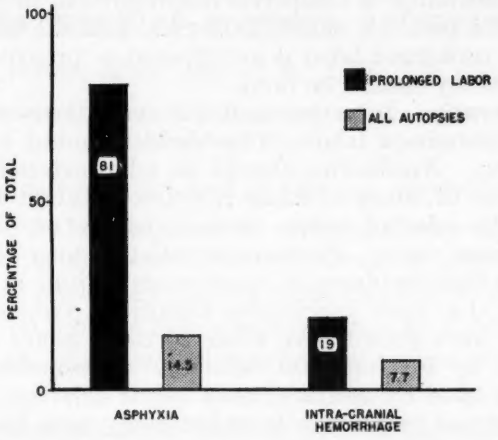

Fig. 4.—Graph showing that fetal deaths from asphyxia were 5 times as common in cases of prolonged labor. Deaths from intracranial hemorrhage were two and one-half times more common in this group.

Maternal Morbidity and Mortality

Thirty-one patients, 58 per cent, were classified as being morbid by the standard criteria, the principal causes being endometritis, cystitis, and septicemia. There was 1 case of peritonitis and 1 of femoral thrombophlebitis.

There was 1 maternal death occurring in the preantibiotic era in a 30-year-old primigravida with severe pre-eclampsia who had a 45-hour labor before a cesarean hysterectomy became necessary. Death occurred 48 hours postoperatively, autopsy revealing a hemolytic streptococcic septicemia with pelvic peritonitis, pneumonia, and acute bacterial endocarditis.

Comment

The purpose of this study was to investigate the cause of fetal mortality associated with prolonged labor. It is realized that there are in addition a number of infants who survive prolonged labor with permanent cerebral damage which might be considered as representing an even more disastrous outcome. These 53 fetal and neonatal deaths, however, comprise the bulk of the grossly mismanaged prolonged labor cases in this hospital subject to a relatively thorough analysis.

This study, together with the accumulated experience of the Boston Lying-in Hospital, suggests the following important points in the management of prolonged labor:

1. *Recognition.*—The primary error has been the failure to recognize the presence of ineffectual labor. Constant vigilance together with a high index of suspicion is necessary to make the diagnosis promptly.

2. *Analgesia.*—Heavy doses of analgesic drugs should be avoided in suspicious cases especially during the early part of the first stage.

3. *Rupture of the Membranes.*—Induction of labor by rupture of the membranes should be utilized only in the presence of an amenable cervix and a

normal presentation. When the vertex is well engaged, disproportion is absent, and labor is slow, the advisability of rupturing the membranes should be considered.

4. Sterile Pelvic Examination.—When progress is questionable or has ceased, a sterile pelvic examination should be performed to survey the status of the cervix and membranes and the possibility of obstructions or malpresentation.

5. X-ray.—The possibility of fetopelvic disproportion should always be considered, even though the pelvis is clinically normal and the infant of usual size. In every case in which prolonged labor is anticipated or progress has become slow or ceased, x-ray pelvimetry should be done.

6. Supportive Therapy.—Intravenous fluids and sedatives should be administered as indicated throughout labor. The bladder should be kept empty and adequate enemas given. Antibiotics should be administered after 8 hours of ruptured membranes or 12 hours of labor if delivery is not imminent.

7. Stimulation.—In selected cases, in the absence of disproportion, malpresentation, and extreme parity, Pituitrin stimulation may be judiciously used.

8. Delivery.—The high incidence of intracranial injury in difficult deliveries in this series suggests that such procedures should be avoided. Peckham[3] and Douglas and Stander[2] have shown that, after 20 to 30 hours of labor, the fetal mortality is increased by instrumental delivery. Reasonable effort should be expended to terminate labor by means of easy pelvic delivery. Cesarean section in this particular group of patients will undoubtedly save many fetal lives.

Summary and Conclusions

1. An analysis of 1,233 fetal autopsies occurring in the Boston Lying-in Hospital and Richardson House during the years 1931 through 1950 is presented.

2. The leading causes of fetal death in this group were: (1) maternal factors (23.1 per cent), (2) congenital malformations (16.4 per cent), and (3) asphyxia (14.6). Intracranial hemorrhage occurred in 7.8 per cent of the cases.

3. During this same period there were 53 fetal deaths which were associated with prolonged labor. Asphyxia was the major pathologic finding in 79 per cent, usually due to intrauterine infection. The remaining 21 per cent were due to intracranial hemorrhage, often related to traumatic delivery.

4. The maternal morbidity in the prolonged labor group was 58 per cent, and there was one maternal death.

5. A plan for the management of prolonged labor is outlined.

The authors wish to thank Dr. Arthur T. Hertig, who has continuously directed the Pathological Laboratory of the Boston Lying-in Hospital since 1931, and Dr. Duncan E. Reid for their constructive criticism in the preparation of the manuscript.

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THE USE OF NEW VERATRUM PREPARATIONS IN THE TREATMENT OF TOXEMIA OF PREGNANCY*

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THE present widespread interest in the use of veratrum derivatives in the treatment of hypertensive diseases, especially toxemia of pregnancy, has resulted in a number of new and improved veratrum preparations on the market. The inadequacies of previously used extracts, i.e., lack of sterilization, instability, complexity, and disagreeable side reactions, have to a certain extent been overcome. The ultimate pharmacologic achievement, that of a pure single alkaloid with minimal side effects that can be synthesized, has not become a reality as yet, although purified alkaloids such as protoveratrine have recently been obtained in a limited quantity.

It was to ascertain what advantages, if any, were present in the extracts Verenteral and Veraflex that the present study was undertaken.

Verenteral, a sterile propylene glycolaqueous tincture of the crude drug veratrum viride, is standardized in rabbits and dogs. The end point of the assay has been that dose required to produce a 30 per cent reduction in the mean control blood pressure. It is stable in undiluted form for at least one year and is intended for intravenous use. Its companion drug, Veraflex, which is for intramuscular use, is prepared in much the same manner except that it is a more concentrated extract in order to permit the injection of a smaller quantity with the same hypotensive effects.

Material and Method

The material consisted of 5 normotensive patients who served as controls, 35 pre-eclamptic, and 3 convulsive eclamptic patients. The ages of these patients varied from 18 to 35 years. Their weight was not taken into consideration in the selection of dosage. Other patients with essential hypertension associated with pregnancy and pre-eclampsia superimposed on essential hypertension received the drug as part of their routine treatment but were not included in this series.

The criteria for the diagnosis of pre-eclampsia was that previously outlined in publications from this department.[1] All the patients were on the obstetrical ward at bed rest. They received no other medication prior to being treated with the two extracts. Some were in labor but all were given a one- to two-hour rest period whenever possible before treatment was started.

The standardization of dosage of Verenteral and Veraflex in human subjects was performed on 5 normotensive and 25 pre-eclamptic patients following the method previously described by Assali.[2] In its essence, this method consisted

*This work was supported by a grant from Irwin, Neisler & Company, Decatur, Ill., who supplied the Verenteral and Veraflex used in the study.

of administration of small intravenous doses of the drug every 10 to 15 minutes until a drop in the blood pressure to normal levels was achieved (Fig. 1). Thereafter, the total amount was given in one single dose. It was found that the effective intravenous dose of Verenteral was 1 c.c. and the intramuscular dose of Veraflex was 0.2 c.c. These findings were then utilized in the treatment regime of the toxemic patients as follows:

A. A continuous intravenous infusion of 5 per cent glucose in water was started a few hours after the patient's admission to the hospital. This was intended to hydrate the patient and to permit the intravenous administration of the drug.

B. A single injection of 1 c.c. of Verenteral diluted in 10 c.c. of 5 per cent glucose in water was given slowly over a 2- to 3-minute period. This injection was given through the infusion tubing in order to obviate a second puncture.

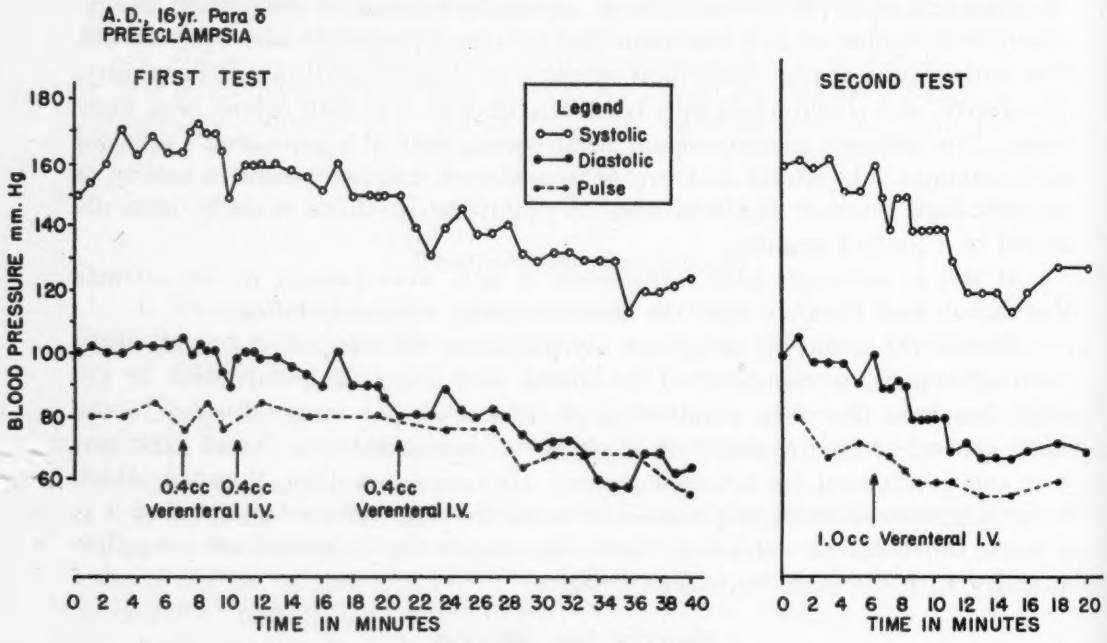

Fig. 1.—Standardization of intravenous Verenteral. *Note.*—The cumulative effect of 3 doses of 0.4 c.c. Verenteral on a pre-eclamptic patient's pulse and blood pressure is essentially the same as one acute dose of 1 c.c. of Verenteral.

C. Forty-five minutes to one hour later, Verenteral was added to the intravenous infusion in the amount of 1 c.c. per 100 c.c. of 5 per cent glucose in water and the intravenous allowed to run at 75 c.c. to 100 c.c. per hour. Thus, a rate of approximately 1 c.c. of Verenteral per hour was given.

D. Blood pressure and pulse rate were taken every minute for the first 30 minutes and every one-half to 1 hour thereafter.

E. Five c.c. of 50 per cent magnesium sulfate were given intramuscularly within the first hour and continued every 6 hours for the duration of the treatment (two eclamptics received 10 c.c. doses).

F. The acute injection of 1 c.c. was repeated within 30 minutes if the effect of the drug appeared to be minimal (this was necessary in one eclamptic patient only).

G. The level of the hourly blood pressure indicated the necessity of speeding up or slowing down the intravenous drip as the readings rose and fell, respectively.

H. When labor or persistent vomiting occurred, a second intravenous infusion of 5 per cent glucose and water was started in the other arm for the purpose of nutrition and hydration. The total daily amount of water administered to the patient varied from 3 to 5 L.

I. After 8 to 48 hours of intravenous therapy, this route was discontinued and intermittent deep intramuscular injection of Veraflex substituted in the amount of 0.2 c.c. every 2 to 4 hours until delivery.

J. The drug was also given intramuscularly for 2 to 3 days in the postpartum period in order to maintain the blood pressure at normal levels, thus preventing any toxemic complications.

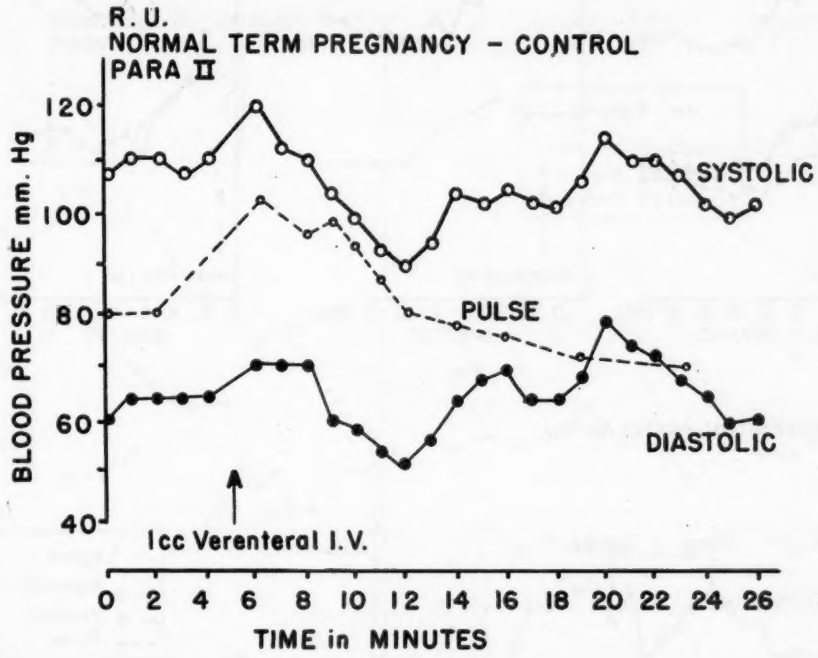

Fig. 2.—Effect of 1 c.c. of intravenous Verenteral on a normal pregnant patient at term. Note the absence of response on the pulse and blood pressure in these normal subjects when given routine therapeutic doses of Verenteral.

Results

1. Normotensive Pregnant Subjects.—

In this group of patients, it was found that 1 c.c. of Verenteral invoked a reduction in the diastolic blood pressure of approximately 10 mm. Hg (Fig. 2). No nausea or vomiting occurred in this group. This confirms previous findings with other preparations of veratrum.

2. Pre-eclamptic Patients.—

One c.c. of Verenteral, regardless of the weight of the patient, lowered the diastolic blood pressure from 15 to 45 mm. Hg (average 28 mm., Fig. 3). Nausea and vomiting occurred either immediately or at some time during the therapy in 15 of the 35 patients. Burning sensation, diaphoresis, and bradycardia were always present. The latter was easily controlled with the intravenous injection of $\frac{1}{200}$ grain of atropine. This, however, was not necessary except in one patient in whom the pulse fell to 40 beats per minute. The vasodepressor effect occurred within the first 10 minutes after the injection, reaching the lowest point after 5 to 7 minutes and continuing for 15 minutes to one

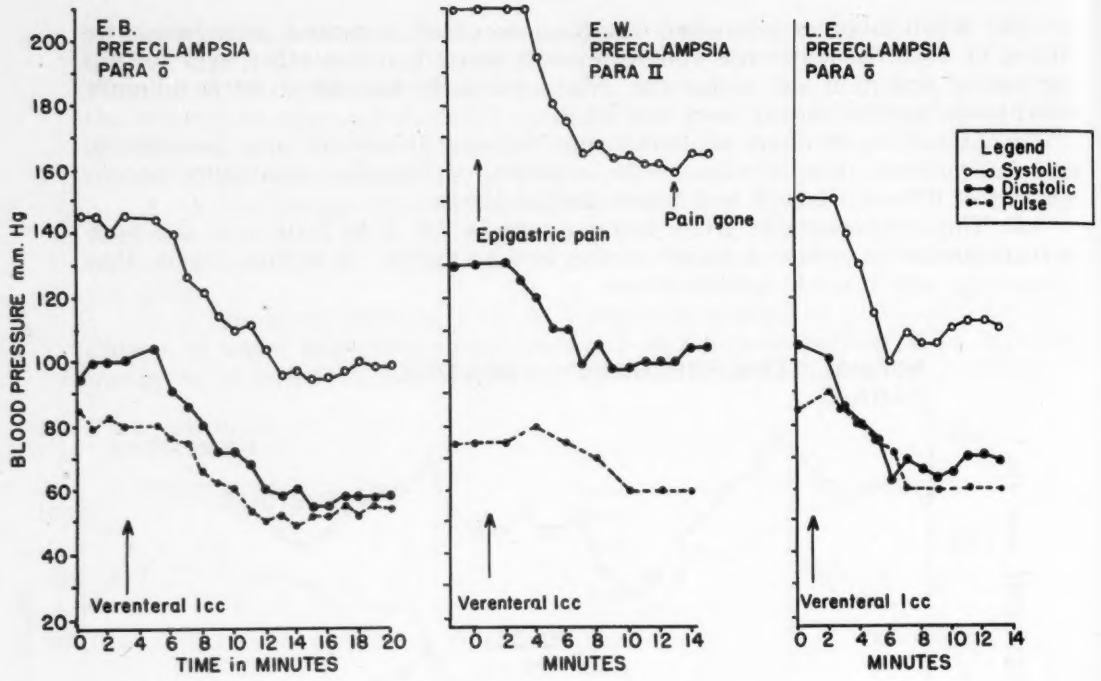

Fig. 3.

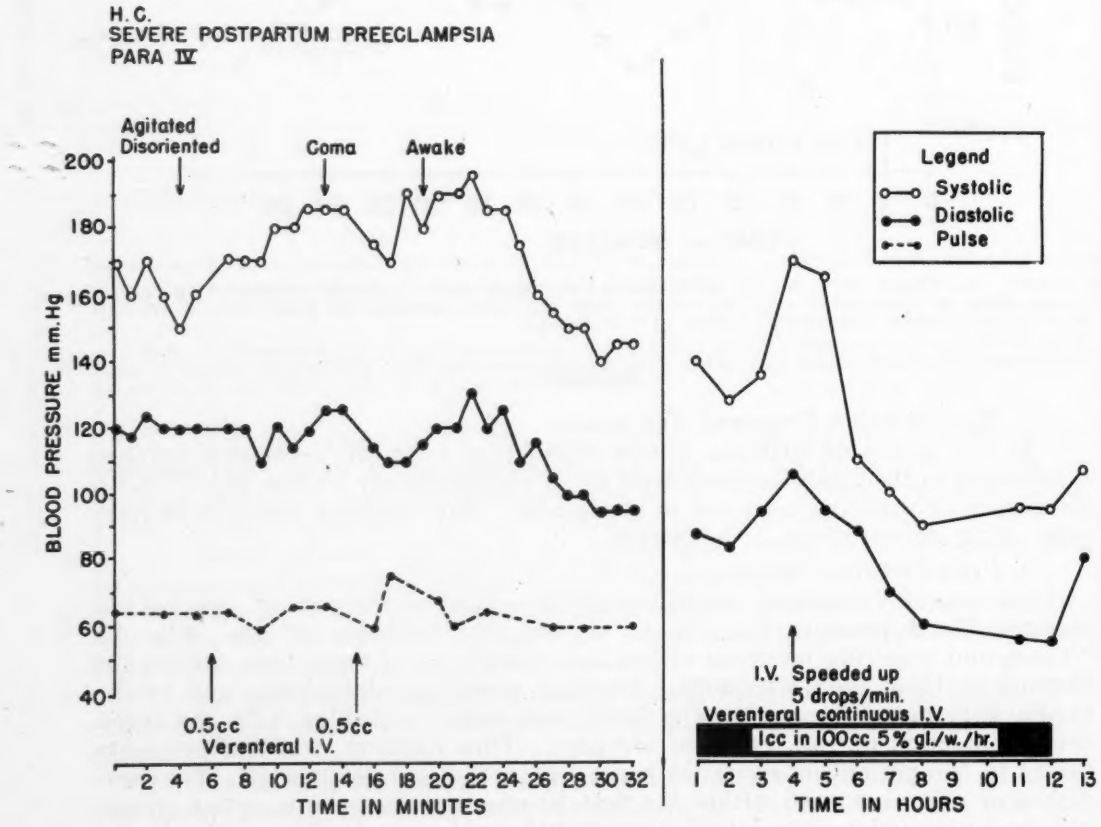

Fig. 4.

(For legends, see opposite page.)

and one-half hours. With the continuous intravenous medication, occasional bounces in the blood pressure occurred when the intravenous infusion was slowed down or speeded up inadvertently (Figs. 4 and 6). However, in general, the blood pressure was maintained within the normal ranges by regulation of the rate of the infusion (Figs. 4, 5, 6). During the transition from intravenous to intramuscular medication, a period of 1 to 3 hours was required before the absorption rate and the patient's individual tolerance to the different medication

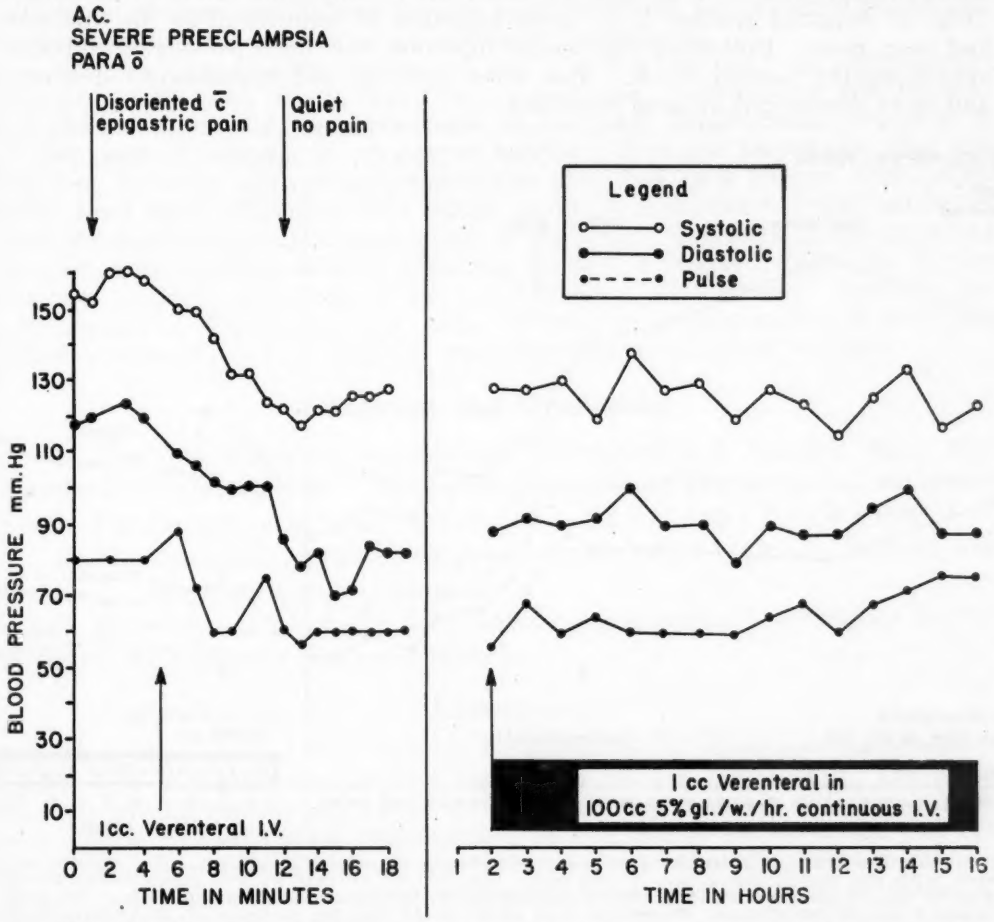

Fig. 5.—*Left,* Effect of 1 c.c. of Verenteral intravenously on the blood pressure and pulse of a pre-eclamptic patient. *Note.*—A striking change occurred in the symptomatology concurrent with the blood pressure drop. The disoriented patient with epigastric pain became oriented and quiet with no epigastric pain at all.

Right, Effect of 1 c.c. of Verenteral in 100 c.c. of 5 per cent glucose in water per hour on the blood pressure and pulse of the above patient. *Note.*—For sixteen hours this patient had perfectly maintained blood pressure.

Fig. 3.—Effect of 1 c.c. of intravenous Verenteral on the blood pressure and pulse of three pre-eclamptic patients. *Note.*—The peak effect occurred within the first 10 minutes. Once the dosage was established, the results on all pre-eclamptic patients were quite similar. A dramatic disappearance of epigastric pain occurred in the patient E. W.

Fig. 4.—*Left,* Effect of divided doses of Verenteral 0.5 c.c. given twice intravenously on the blood pressure and pulse of a wildly agitated postpartum pre-eclamptic patient. Note the difference in time interval between injection and effect as contrasted to Fig. 3.

Right, Effect of continuous intravenous infusion of Verenteral, 1 c.c. in 100 c.c. of 5 per cent glucose in water per hour. Note the temporary blood pressure spike which was brought easily back to normal levels by speeding up the rate of flow of the infusion. The patient was controlled for 13 hours by this method before changing to intramuscular Veraflex, 0.2 c.c. every 2 to 4 hours. No tolerance to the effect of the drug was developed.

were determined. Deep intramuscular injection had to be resorted to since much local pain occurred when it was given superficially. In two pre-eclamptic patients, one with headache and one with epigastric pain, the symptoms were relieved after the initial acute intravenous injection (Figs. 3 and 5).

3. Eclamptic Patients.—

In all three cases, the blood pressure and convulsions were well controlled within less than two hours after the administration of the drug. The diastolic blood pressure fell 30 to 45 mm. Hg below the pre-injection levels. One patient (Fig. 6) required another 1 c.c. acute injection 30 minutes after the first dose had been given. Following this second injection, the blood pressure dropped to approximately normal levels. The three patients had spontaneous deliveries and were discharged in good condition.

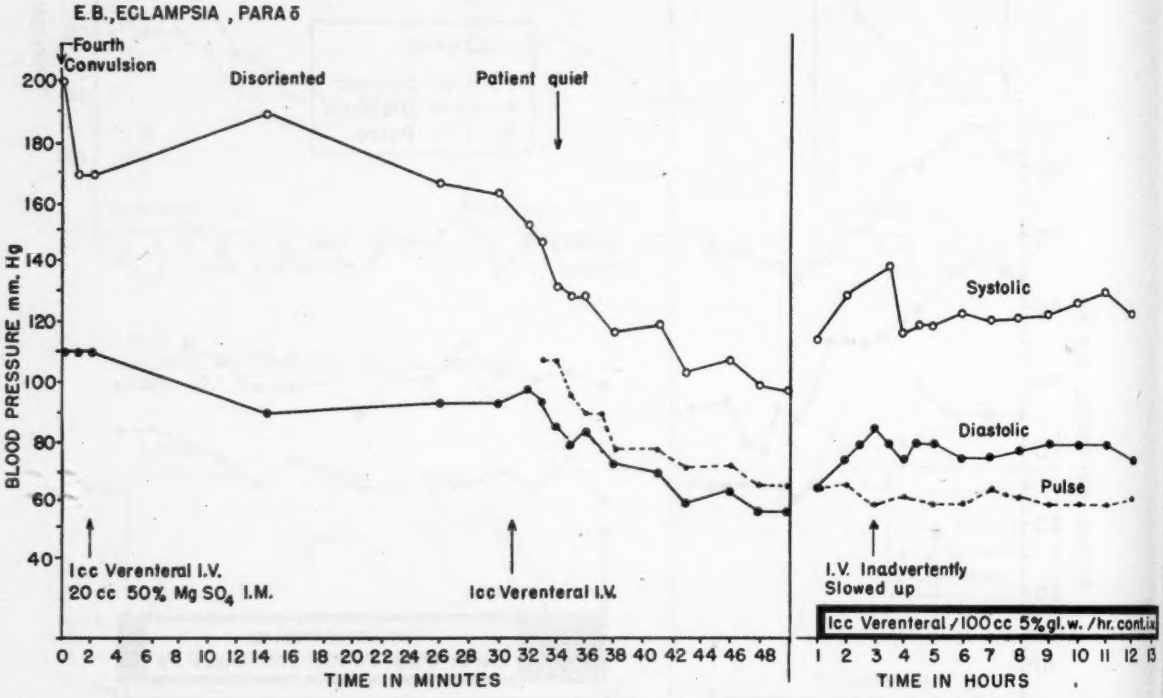

Fig. 6.—Effect of Verenteral in the treatment of an eclamptic patient. The patient was seen with the fourth convulsion in progress. One c.c. of Verenteral was given intravenously and 20 c.c. of 50 per cent magnesium sulfate given intramuscularly immediately. An additional 1 c.c. of intravenous Verenteral was given in 30 minutes because of inadequate blood pressure response. From then on the patient became quiet, no more convulsions occurred, and the blood pressure dropped to normal levels. The continuous intravenous infusion of 1 c.c. of Verenteral in 100 c.c. of 5 per cent glucose per hour gave excellent results with the exception of a brief period of technical difficulty with the infusion.

Comment

The ideal drug for the treatment of toxemia of pregnancy has not been found and probably will await the discovery of the basic etiological process involved. As an adjunct in the treatment of eclampsia and pre-eclampsia, veratrum has proved to be of decisive value. The record at Cincinnati General Hospital of 205 consecutive cases of convulsive eclampsia treated with this drug with only one maternal death attributable to eclampsia per se attests to its efficacy. Although much remains to be learned concerning its pharmacologic action, the vasodepressor effect is well established. From a large number of investigations[3-6] aimed at elucidating the mechanism of the vasodepressor effect

of veratrum, it seems that this drug acts by producing arteriolar vasodilatation without affecting the venous side of the circulation. Thus, a decrease in the peripheral resistance and a drop in the blood pressure is obtained without any marked effect on the cardiac output or any postural hypotension. This integrated hypotensive effect of the veratrum preparations appears to be the most rational approach in the basic therapy of a disease such as toxemia of pregnancy in which presumably the predominant pathophysiological phenomenon is arteriolar vasoconstriction.[7] The breakdown of the complex alkaloids and the utilization of separate alkaloids such as protoveratrine[8] may advance our knowledge concerning the pharmacologic action of these drugs.

The new preparations Verenteral and Veraflex represent an improvement over previously used ones in that they are sterilized, standardized, and reasonably stable. Clinically, they produced an adequate vasodepressor response in all the cases of toxemia of pregnancy treated. It is our impression that less vomiting occurred with these preparations than had been present with previously used ones. Although this emetic action is disturbing to the patient it does not seem to indicate a toxic effect of the drug. The work of Meilman and Krayer[8] with various isolated alkaloids showed a marked difference in the various alkaloids with regard to vasodepression and emesis. Possibly the preparation of Verenteral may have resulted in a composition of alkaloids which produces a more favorable response than the natural mixture.

Summary and Conclusions

1. Two new veratrum preparations, Verenteral and Veraflex, have been described and standardized. The intravenous dose of Verenteral is 1 c.c. every hour. The intramuscular dose of Veraflex is 0.2 c.c. every 2 to 4 hours.

2. The treatment regime of 35 pre-eclamptic and 3 eclamptic patients was described. The results were presented.

3. Verenteral and Veraflex were found to be adequate preparations for the treatment of eclampsia and pre-eclampsia.

Addendum

After this paper had been submitted for publication, 12 pre-eclamptic subjects and 3 patients with convulsive eclampsia were treated with the same preparations. Two of the eclamptic patients required only 0.5 c.c. of Verenteral intravenously in order to reduce the blood pressure to normal levels. The remaining patients required the full amount. In view of the finding that some patients are sensitive to the action of the drug, it is advantageous to start the treatment first with 0.5 c.c. of Verenteral intravenously and repeat the dose as indicated by the fall in blood pressure.

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CYCLIC BIOCHEMICAL CHANGES IN THE HUMAN ENDOMETRIUM

With Special Reference to the Fibrinolytic Enzyme*

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DURING the past forty years the cyclic morphologic changes in the human endometrium and their relationship to the ovarian cycle have been described many times in meticulous detail. There is no doubt, of course, about the role of estrogens in causing endometrial growth or of progesterone in causing the secretory changes. We are still ignorant, however, about the mechanism of hormone action. Why should the uterine mucosa respond to estrogens so much more than intestinal mucosa, for example? Do steroids exert their influence upon cells by altering membrane permeability, by combining with some protein to form an enzyme, or by means totally unknown? What are the biochemical changes which underlie morphologic alterations?

These are questions which must ultimately be solved with the tools of biochemistry. They are questions which have led many morphologists into the field of histochemistry and have encouraged even gynecologists to delve into enzymology. Most chemical data on human endometrium, with a few exceptions, have been reported in the last few years so that any general statements about cyclic patterns must be regarded as tentative. The purpose of this report is to summarize our knowledge, and to contribute pertinent data regarding the cyclic fluctuation in the endometrial concentration of a fibrinolytic enzyme.

Relation of Endocrine Changes to Biochemical Patterns

The correlation of ovarian hormone changes with the morphologic picture of the endometrium in a normal menstrual cycle is so widely known that it need not be reviewed here. Some of the chemical constituents of the endometrium are probably uninfluenced by the endocrine cycle. This may be true of water and electrolytes, for the recent report of Stuermer and Stein[1] suggests that the concentration of free water in human endometrial samples is about 82 per cent and does not change appreciably in the menstrual cycle. If this is true, it indicates that the appearance of "edema" in the late secretory phase may be due to the intercellular accumulation of a mucoid substance containing about the same quantity of water as the cells.

The various proteins, fats, and carbohydrates which have been studied show fluctuations which appear to fall into four patterns (Fig. 1).

The first pattern is exemplified by the endometrial concentration of beta-glucuronidase. Odell and Fishman[2] examined the content of this enzyme in 36 endometrial samples and concluded that it increased progressively under the

*Supported in part by a grant from the Edwards Fund, University of California.

influence of estrogen, then fell during the last four or five days before menstruation, i.e., during estrogen withdrawal. This change appeared to be independent of progesterone. Beta-glucuronidase is thought to regulate the conjugation of steroids with glucuronic acid as well as the hydrolysis of glucuronides.[3] Working with mice, Harris and Cohen[4] found that progesterone caused a reduction in the beta-glucuronidase activity of vagina, kidney, liver, and spleen. They also noted that while castration caused a marked reduction in the uterine content of this enzyme, the activity of vaginal tissue was unchanged. This does not support the contention that glucuronidase activity is correlated with the processes of cellular proliferation.

The second pattern is likewise concerned with estrogens and not with progesterone, but differs from the first in that estrogen withdrawal produces the highest endometrial concentration. The fibrinolytic enzyme to be described below falls into this group. It would seem that catabolic processes, rather than anabolic, are concerned with the increased amounts of this protease. Caffier[5] placed bits of human endometrial tissue upon the surface of a Loeffler's plate, which consists of heat-coagulated blood serum, beef broth, and glucose. By noting the depressions produced he estimated the proteolytic activity, and concluded that it was very low in the proliferative phase and high in the premenstrual phase. In accordance with our own results, the highest values were noted during uterine bleeding, regardless of whether the endometrium was proliferative or progestational.

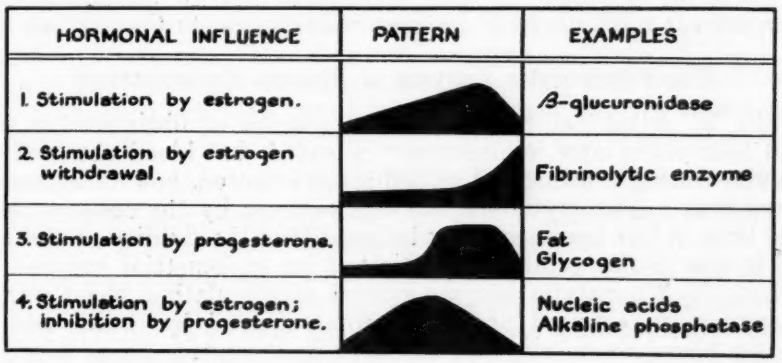

Fig. 1.

The third pattern consists of the biochemical changes brought about by progesterone. The accumulations of lipids and glycogen within the glandular epithelium during the secretory phase seem to represent examples of progesterone influence. According to Gillman,[6] the accumulation of those lipids which can be stained by scarlet red in the base of the glandular cells is a measure of progesterone influence. His conclusions are based upon a histochemical study of 140 normal and abnormal endometria. The influence of progesterone upon intracellular glycogen is well known, and a good description of the cyclic changes has been presented by Arzac and Blanchet.[7]

The fourth pattern consists of those changes which are stimulated by estrogens but which regress under the influence of progesterone. This appears to be true for ribonucleic acid and also for alkaline phosphatase. The intracellular ribonucleic acid concentration provides an index of the rate of protein synthesis. Atkinson and associates[8] utilized histochemical methods for determining the nucleic acids in human endometrium and found increasing quantities during the proliferative growth phase, then a gradual decrease and virtual disappear-

ance just before menstruation. This was confirmed by Stein and Stuermer,[9] who used direct chemical analyses. In contrast to ribonucleic acid, the desoxyribonucleic acid concentration showed a slight but steady increase throughout the cycle.

A similar pattern is noted in the case of alkaline phosphatase. This enzyme (or group of enzymes) supplies necessary phosphate ions for a number of important processes, including the metabolism of nucleoproteins and lipids and the breakdown of glucose-phosphates in the carbohydrate cycle. The histochemical distribution in the endometrium has been reviewed recently by Atkinson.[10] There is a definite peak about the time of ovulation, followed by a steady decline. That this is related to the ovarian cycle was demonstrated by showing that phosphatase increases in the endometrial glands of the castrate monkey following estrogen administration, then diminishes during subsequent progesterone administration. Similar findings have been reported by Hall.[11]

Fluctuations in alkaline phosphatase and in ribonucleic acid content do not always parallel each other, for, in endometrial carcinoma, there is a further increase in nucleic acids whereas the alkaline phosphatase disappears. While this report is chiefly concerned with the endometrial cycle, it should be noted in passing that the endocervical epithelium shows changes in histochemical reactions which vary with the hormonal status, as described by Wislocki, Bunting, and Dempsey.[12]

Harris and Cohen[4] found that the esterase activity of the uterus and vagina of the mouse was markedly increased by castration and reduced by the administration of estrogen. If this were confirmed on human endometrium, it would represent a fifth type of biochemical response to the ovarian hormones.

The Fibrinolytic Enzyme of Human Endometrium

In 1910, W. Blair Bell[13] described the absence of fibrinogen in menstrual blood, and four years later Whitehouse[14] reported that blood obtained from the uterine cavity during a menstrual period always clotted, but subsequently lysed. He believed that a fibrinolytic enzyme was secreted by the endometrial glands. Since that time, it has been generally believed that the fluidity of the menstrual discharge is due to the proteolytic action of an endometrial enzyme.[15, 16] An activation of the fibrinolytic enzyme system of circulating blood during menstruation and in toxemia of pregnancy was reported by Smith and Smith,[17] although this phenomenon may be unrelated to the intracellular fibrinolysin of the endometrium. They expressed the view that the enzyme of menstrual blood resulted from the breakdown of endometrial cells. The fibrinolysin, however, is present in the endometrium in appreciable quantities before the stage of regression and may conceivably be concerned with the process of disintegration and shedding.

Methods of Study

In an effort to study this phenomenon, some quantitative method of measuring tissue fibrinolysin had to be developed. Under appropriate conditions, the concentration of an enzyme is proportional to its activity, and the latter may be measured in one of two ways: by observation of the rate of disappearance of the substrate or by measurement of the rate of appearance of a product. In the case of fibrin or fibrinogen, the products of their lysis cannot readily be measured. We therefore selected fibrinogen as our substrate and used as a measure of enzyme activity the rate of fibrinogen disappearance.

The method finally adopted may be briefly described: The tissue extract was prepared by washing the fragments of endometrium thoroughly in order to remove blood, then grinding with sand in a mortar and extracting with a small amount of distilled water. The amount of material extracted was determined by

drying exactly 1 ml. of the extract to a constant weight at 90° C. This was done so that enzyme activity could be expressed in "units" for each milligram dry weight of tissue extract.

The activity of this extract was first estimated by adding 0.5 ml. to a "pilot tube" containing fibrinogen, incubating at 28° C., and removing aliquots periodically in order to determine the approximate speed of the reaction. The time estimated for 50 per cent lysis in the pilot experiment was then used for the final incubation. This method of varying the time of the incubation could not be used for an accurate assay because there was a progressive denaturation of the enzyme with time and because the percentage of fibrinogen destroyed was not proportional to time owing to the presence of inhibitors. It was therefore necessary to use varying dilutions of enzyme for a constant period of time.

Into each of six tubes were placed 2 ml. of a 2 per cent solution of bovine fibrinogen (Parke, Davis), buffered with imidazole to pH 7.25. The first two tubes were used as controls, one containing added saline and the other containing 0.5 ml. of heat inactivated extract. (This was necessary because a certain proportion of extract is incorporated in any given amount of fibrin, and a correction factor is needed.) Quantities varying from 0.1 ml. to 1 ml. of extract were then added to the remaining four tubes, together with a few drops of toluene, the final volume was adjusted to 3 ml. with saline, and all were incubated at 28° C. for the time previously determined. At the end of the incubation, 10 ml. of water containing 10 mg. of thrombin (Parke, Davis, topical) were added to each tube, and after one hour the fibrin was collected on glass rods, dried to constant weight on tared cover slips, and weighed. A percentage of the weight of the tissue extract and the thrombin (the same as the percentage of fibrin remaining) was subtracted, because both proteins were adsorbed to fibrin.

The amount of endometrial extract which would cause the lysis of 50 per cent of the fibrinogen was then estimated by interpolation (or in some cases by extrapolation). One unit of fibrinolytic activity was arbitrarily defined as $\frac{T \times E}{693}$, where T = the incubation time in hours, and E = the dry weight in milligrams of extract needed to lyse half of the fibrinogen. (The value 693 is derived from the equation for a first order reaction.)

The difficulties encountered with this method were due to the fact that all extracts contained variable amounts of active enzyme inhibitor as well as active enzyme, both existing in a mass law equilibrium with each other. Diluting an extract usually increased its activity up to a certain point, because the inhibitor action is affected much more by dilution than the enzyme action. With some tissues, such as human placenta, only inhibitor can be demonstrated. In practice, we accepted the values for those dilutions of the extract which demonstrated the highest activity and which approached most closely a first order reaction. For estimating the inhibitor content of the extracts (antifibrinolysin), we used large amounts of a purified fibrinolytic enzyme, and measured its inhibition by the method of Guest, Daly, Ware and Seegers.[18]* We were unable to effect a chemical separation of the enzyme and its inhibitor, and until this can be done no method could give absolute values for total tissue enzyme. Our values are subject to a variation of at least 50 per cent; nevertheless, the observed differences in various stages of the menstrual cycle are sufficiently great so that we may say with certainty that the highest concentrations occur in the premenstrual and menstrual phases of the cycle.

Results

The values obtained in endometrial curettings are shown in Fig. 2. These were independently dated in the menstrual cycle by Dr. Leo Doyle, who used

*We are indebted to Mr. E. C. Loomis of Parke, Davis & Company, Inc., for supplying the fibrogen, fibrinolysin, and antifibrinolysin (cf. Arch. Biochem. 12: 1, 1947, and 20: 444, 1949).

histologic criteria. The values for a group of abnormal endometria showing endometrial hyperplasia without evidence of progesterone influence are illustrated on the right side of the chart. These values were high, suggesting that progesterone is not concerned with the concentration of this particular enzyme.

The clinical results suggest that estrogens are in some way responsible for the increased fibrinolytic enzyme concentration. This was tested experimentally by measurement of the activity of the uteri of rabbits which had been treated in various ways. The mean value for uteri of intact rabbits was 3.5 units per milligram dry weight of extract. The intramuscular administration of 5 mg. of progesterone daily for five days did not increase this activity. A month after castration, the average activity of rabbit uteri was found to be 1.7 units per milligram, showing that the removal of estrogens ultimately leads to a reduced activity. Four intact rabbits were given 750 I.U. of estrogen (Neo-Amniotin) intravenously each day for four days and sacrificed on the day of the last injection. The uterine activity ranged from 2.3 to 5.0 units per milligram. Nine rabbits were given the same treatment, but a period of 4 to 6 days was allowed to elapse after the last injection before they were sacrificed. The uterine activities ranged from 4.5 to 13.0 units per milligram (average = 6.8), indicating that the period of estrogen withdrawal produces the highest enzyme concentration.

FIBRINOLYTIC ACTIVITY OF HUMAN ENDOMETRIUM

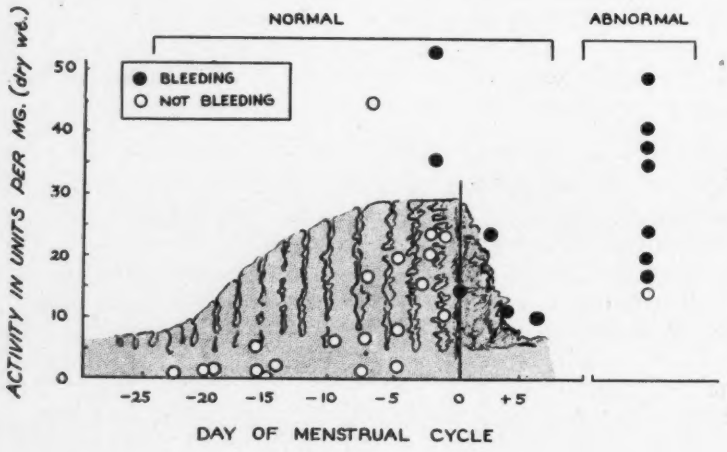

Fig. 2.

There are, of course, two possible explanations for a high activity: (a) an increased amount of enzyme in the tissue, or (b) a reduction in the amount of inhibitor (antifibrinolysin). In several of the rabbit experiments, therefore, the enzyme and inhibitor concentrations were measured in the same extracts; and it was found that they were directly, rather than inversely proportional to each other. This would indicate that high activities are due to increased total enzyme concentration.

The data from the rabbit experiments thus confirm the deductions made from the human material, namely, that the prior action of estrogens, followed by a withdrawal of this growth-promoting influence, is responsible for the highest content of endometrial fibrinolysin. Whether this enzyme is concerned with the fragmentation of the endometrium during menstruation is speculative, but there

is little doubt about its importance in causing the fluidity of menstrual or lochial blood. If in vitro measurements conducted at 37° C. can be applied to the situation in vivo, it is estimated that half of any plasma fibrinogen coming into contact with an endometrium which has an activity of 25 units per milligram would be lysed in eight minutes. Considering the high content of endometrial thromboplastin, the blood would clot much faster than that, and subsequent lysis of the fibrin would take place in the tissue spaces, uterine cavity, or in the vagina. The rate of lysis would depend not only upon the amount and activity of endometrial debris carried away by the blood, but the volume of blood in which it is contained and the length of time that the clot remains within the body.

Summary

The biochemical changes occurring in the human endometrium during a menstrual cycle have been reviewed and classified into four patterns. The amount of beta-glucuronidase parallels the estrogen curve, whereas the content of protease is greatest during the regressive phase of estrogen withdrawal. The intracellular concentration of fat and of glycogen follows the progresterone pattern, while the amount of ribonucleic acid and alkaline phosphatase present in the endometrium increases under the influence of estrogen, then declines with the addition of progesterone.

A method for measuring the concentration of fibrinolytic enzyme in tissue is described. When applied to human endometrial samples, it was found that the fibrinolytic activity increased in the latter part of the menstrual cycle, regardless of progesterone influence, and was highest during the bleeding phase. The stimulative influence of estrogens and of estrogen withdrawal upon the fibrinolytic activity of uterine extracts was confirmed in rabbits. Increased activity following estrogen administration is due to an increase in total enzyme concentration and not to a reduction of antifibrinolysin. Endometrial fibrinolysin bears a relation to the fluidity of menstrual blood and might be concerned with the process of endometrial disintegration and shedding.

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THE CARE OF THE POSTPARTUM CERVIX

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THE care of the postpartum cervix is carried out by a variety of methods; these include no treatment, douches from the tenth postpartum day, and cauterization of the cervix at the first postpartum visit. Regardless of the method selected, the obstetrician endeavors to make certain that the cervix is in normal healthy condition by the time of the last postpartum visit. The most important detail in the care of the postpartum cervix is the treatment of erosions. Whether or not these denuded areas form the precursor for later carcinoma, there is no question that they are the locus of a chronically infected, irritating discharge that is disturbing to the patient. Because of the frequent appearance of cervical erosion as a complication of the late postpartum period, a study was organized in the postpartum clinic of the Boston Lying-in Hospital to evaluate the efficacy of various types of therapy. This paper presents data on 101 patients with postpartum cervical erosions.

Trauma to the cervix at the time of delivery would seem to be the chief cause of cervical erosion. There is ample evidence to show that difficult forceps operations, breech extraction, manual dilatation of the cervix, and internal podalic versions are associated with a marked increase in cervical lacerations and erosions. The policy at the Boston Lying-in is the practice of conservative obstetrics.[1] For the last two decades high forceps and manual dilatation of the cervix have been abandoned, and the use of midforceps and internal podalic version is increasingly rare.

During eight months covered by this study, the incidence of postpartum erosion at the Boston Lying-in was 10 per cent. Other clinics have reported as high a percentage of erosion as 81 per cent.[2] This difference is undoubtedly due to definition.

Methods and Material

All patients were examined at the eighth postpartum week and the cervix biopsied in those with erosions to rule out the presence of malignancy. This group returned at the tenth postpartum week for definitive treatment of the cervix. No patient was included in the study who had an erosion less than 1.5 to 2 cm. in width, and 75 per cent of those studied extended circumorally from 2 to 4 cm. By limitation of the investigation to erosions that would be considered moderate to severe by any criteria, it was felt that the efficacy of specific therapy could be evaluated. All patients were selected, followed, and treated by the same observer. Each patient was examined at two-week intervals, and the appearance of the cervix carefully described. At first, patients

were assigned in rotation to each of four treatment groups: Group N, a control group which received no therapy; Group S,* a group treated by vaginal instillations of Triple Sulfa Cream twice a day; Group C, a group treated by electrocauterization alone; and Group C & S, a group treated by cauterization and vaginal instillations of Triple Sulfa Cream twice a day. However, it became evident, after three months, that the results in Groups N and S were too poor to warrant further study. Accordingly, all subsequent patients were divided between Group C and Group C & S, and an attempt was made to determine whether Triple Sulfa Cream made any significant difference in the healing of postpartum erosions after cervical cauterization. A few patients did not return after having been assigned to a group, which accounts for the small difference in the number treated by C and C & S.

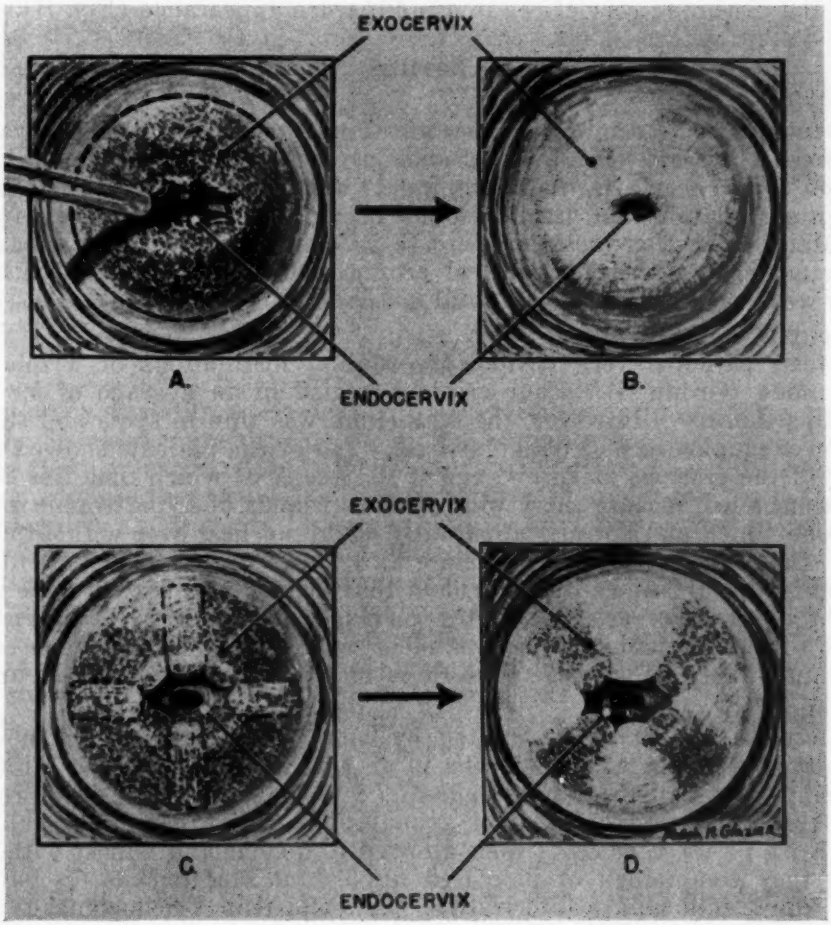

Fig. 1.

Technique of Cauterization

The entire area of erosion on the exocervix was lightly cauterized with the hot cautery (Fig. A, area enclosed in dotted lines). The aim was to level exuberant granulations without destroying the submucosa by too vigorous

*Triple Sulfa Vaginal Cream, supplied by the courtesy of the Ortho Pharmaceutical Corporation, Raritan, New Jersey.

application of heat. This technique resulted in complete healing of the exocervix (Fig. B). Past experience has shown that mere striping of the exocervix (Fig. C) leaves areas of erosion which cannot epithelize because of high granulation tissue (Fig. D).

The endocervix was treated cautiously to avoid stenosis. Usually striping the endocervix once at six and twelve o'clock was sufficient to correct minor degrees of eversion. The cautery was also applied at three and nine o'clock whenever considerable gaping of the cervical os was present (Fig. A, endocervix).

Ectropion of the endocervix was observed in many patients who had suffered an intrapartum laceration of the cervix. When untreated, the patulous and everted endocervix remained chronically inflamed and produced a copious mucoid discharge (Fig. D). Striping of the endocervix helped greatly in restoring the disrupted cervical os to a nulliparous appearance (Fig. B).

Results

Group N.—

Twenty patients comprised the control group, Group N. These were followed for an average of 9.5 weeks and only 6 showed partial healing. The condition of the cervix in the remaining 14 deteriorated; there was piling up of rough granulations and the development of deep fissures in the area of erosion. Many times there was an increase in discharge. It would appear that when a moderate to severe cervical erosion was present at the tenth postpartum week, spontaneous healing did not occur thereafter.

Group S.—

Fifteen patients were treated by vaginal instillations of Triple Sulfa Cream alone (Group S). Four erosions healed in an average of 5.8 weeks under this therapy. However, the epithelium was thin in spots and superimposed on a roughened and irregular base. Ten of the patients showed partial healing of the erosions at an average of 8.1 weeks, at which time this therapy was discontinued because there were obvious islands of hypertrophic granulation tissue which had not and apparently could not heal over without cauterization. One erosion showed no healing at 9 weeks. No further patients were assigned to Group S since it was evident that Triple Sulfa Cream alone was insufficient therapy for erosions of the cervix. Nevertheless, the cervices and vaginas of the patients under treatment with Triple Sulfa Cream seemed cleaner and freer of discharge than those followed in the control Group N.

Group C.—

Thirty-six patients were treated by cauterization alone. Of these, five were partially healed when last seen in an average of 7.4 weeks. Thirty-one were completely healed in an average of 7.8 weeks. Five of these 31 required partial recauterization of indolent granulations before complete healing ensued. None of these patients were allowed to douche and almost without exception they complained of increased unpleasant sanguineous discharge for several days following cauterization. A persistent Trichomonas-type discharge was noted in eight.

Group C & S.—

Thirty patients were treated with cauterization and twice daily instillations of Triple Sulfa Cream. The erosions in this group were all healed in an average of 3.8 weeks. Thus, when sulfa cream was used in conjunction with cauterization, the average healing time was half that of cauterization alone. When the cervix treated with C & S was inspected 2 weeks after cauterization it was remarkably clean, whereas those treated with cautery alone often had an edematous cervix with adherent slough.

Re-treatment Group C & S.—

Fifteen patients who had been failures in Group N or Group S after an average of 10 weeks of treatment were transferred to a re-treatment group of cauterization and twice daily instillations of Triple Sulfa Cream. These were all healed in from three to ten weeks. The average healing time was 5.0 weeks after inception of C & S. Four of these patients needed partial recauterizations at 5, 4, 4, and 6 weeks, respectively, because of islands of high granulations which would not cover over. These may have been the result of initially inadequate cauterizations. The re-treatment group was first cauterized at 20 weeks post partum, and by that time the granulations had become high and fissured. Accordingly, the chance of an incomplete or too extensive cauterization was greater than at 10 weeks post partum. It appeared that the tenth postpartum week was an ideal time to cauterize the cervix.

TABLE I. RESULTS

TYPE OF TREATMENT	NUMBER OF PATIENTS	NUMBER HEALED*	NUMBER PARTIALLY HEALED*	NUMBER SHOWING NO HEALING*
Group N	20	0 at 9.5 weeks	6 at 9.5 weeks	14 at 9.5 weeks
Group S	15	4 at 5.8 weeks	10 at 8.1 weeks	1 at 9 weeks
Group C	36	31 at 7.8 weeks	5 at 7.4 weeks	0
Group C & S	30	30 at 3.8 weeks	0	0
Re-treatment Group C and S	15	15 at 5.0 weeks	0	0

*Time reported is the average period of observation for the group.

Comment

In many respects a cervical erosion resembles a granulating traumatic wound. The higher incidence of erosion in complicated obstetrical procedures reflects the increased trauma which accompanies difficult operative obstetrics. One can suppose that the majority of patients with minor damage to the cervix have complete spontaneous healing within the first postpartum month. However, when a large area of cervical epithelium is lost, while partial spontaneous re-epithelization from the periphery can be observed, this soon comes to indolent arrest. The situation is analogous to delayed healing of a granulating wound of the skin because of "proud flesh," that is, exuberant granulations which are too high to bridge. A clean granulating wound of moderate size heals steadily from the periphery as long as the granulations are of proper height. Therefore, it is necessary to cauterize the 10 week postpartum erosion in order to produce a base which can cover over.

Wound healing on the surface of the body is markedly slowed or stops whenever wound infection is present. The necrotic tissue which results from cauterization forms an ideal bed for bacterial growth. This suggested that the control of secondary invaders of the cervix following cauterization might lead to accelerated healing of an erosion. Triple Sulfa Cream seemed worth while investigating because of its proved bacteriostatic effect.[3] The results showed that when secondary infection was controlled, healing of the cauterized cervix proceeded at a more rapid rate and the patient was discharged sooner than would have been otherwise possible. Furthermore, both subjectively and objectively the use of Triple Sulfa Cream reduced the postcautery discharge.

Summary

Factors affecting the rate of healing of 101 postpartum erosions of the cervix were investigated. Erosions which were present at the tenth post-

partum week did not heal spontaneously. Adequate cauterization of the cervix resulted in complete healing in an average of 7.8 weeks. It was presumed that cauterization reduced exuberant granulations and allowed resumption of epithelial ingrowth from the periphery of the erosion.

The twice daily use of a triple sulfa vaginal cream in conjunction with cauterization reduced the average healing time to one-half that following cauterization alone. It was thought that this reduction in healing time resulted from the control of secondary infection in the cauterized cervix.

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THE HEMODYNAMIC EFFECTS OF RONIACOL*

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IN RECENT literature, there have been few isolated reports on the vasodilator action of Roniacol.[1, 2] It has been suggested that the pharmacologic properties of this drug might produce an increase in the blood flow to the kidneys, heart, and extremities. The present study was undertaken in order to investigate the hemodynamic changes produced by this drug in human subjects, particularly in the pregnant woman. In previous papers[3-6] it was shown that the normal pregnant woman offers an excellent opportunity for studying autonomic blocking and vasodilating agents, due to her increased neurogenic vasoconstrictor tone. Roniacol is converted in the organism to nicotinic acid, but its vasodilating action is not well understood. Chemically it is B-pyridyl-carbinol which is the alcohol corresponding to nicotinic acid.

Material and Method

The material consisted of 18 normal pregnant women, 12 patients with the diagnosis of toxemia of pregnancy, 2 with essential hypertension and superimposed toxemia, and 4 normotensive nonpregnant subjects. All of them were admitted to the obstetrical ward and were at bed rest for some time before the experiment. The diagnosis of toxemia of pregnancy followed the same criteria as outlined in other reports from this department.[3, 4] Roniacol was given to these patients in intravenous doses varying from 50 to 300 mg.

Control determinations of resting blood pressure (sphygmomanometer), pulse rate, and skin temperature were recorded. Skin temperature studies were carried out in a constant room temperature with the use of an electric thermocouple accurate to 0.2 degree. Mannitol and para-aminohippurate clearances for measurements of glomerular filtration rate and renal plasma flow under both water and osmotic diuresis were performed following the methods described elsewhere.[6, 7] The urine concentrations of sodium, potassium, and chloride were also determined by the same methods. Thereafter the drug was given in acute intravenous injection, and the same studies were repeated in periods varying from 20 to 90 minutes. Urine and blood samples were analyzed for their content of mannitol, para-aminohippurate, potassium, sodium, and chlorine by the techniques previously described.

Results

The results are shown in Figs. 1 to 7.

A. Blood Pressure and Pulse Rate.—

1. Normotensive nonpregnant and pregnant subjects: The administration of 100 to 300 mg. of Roniacol invoked insignificant changes in the blood pressure of these two groups of patients. There was usually a slight rise immediately after the injection which was probably due to emotional reaction to the drug.

*This study was supported by a grant from Hoffmann-La Roche, Inc., Roche Park, Nutley 10, N. J., who also furnished the Roniacol.

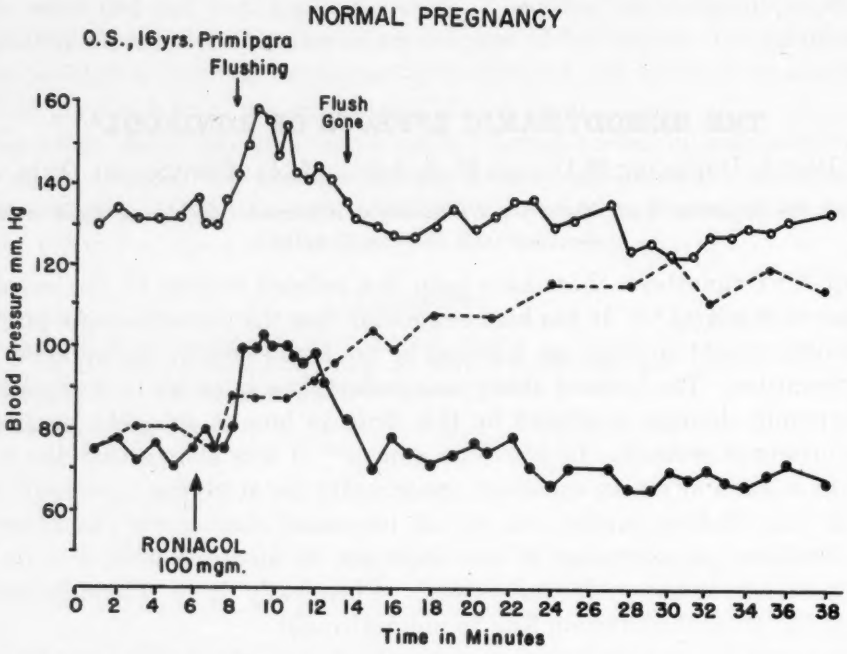

Fig. 1.—The effect of Roniacol on the blood pressure and pulse rate of normal pregnancy at term. The open circles indicate the systolic and the closed circles the diastolic blood pressure. The interrupted line indicates the pulse rate. The initial rise in the blood pressure is probably due to emotional reaction to the drug.

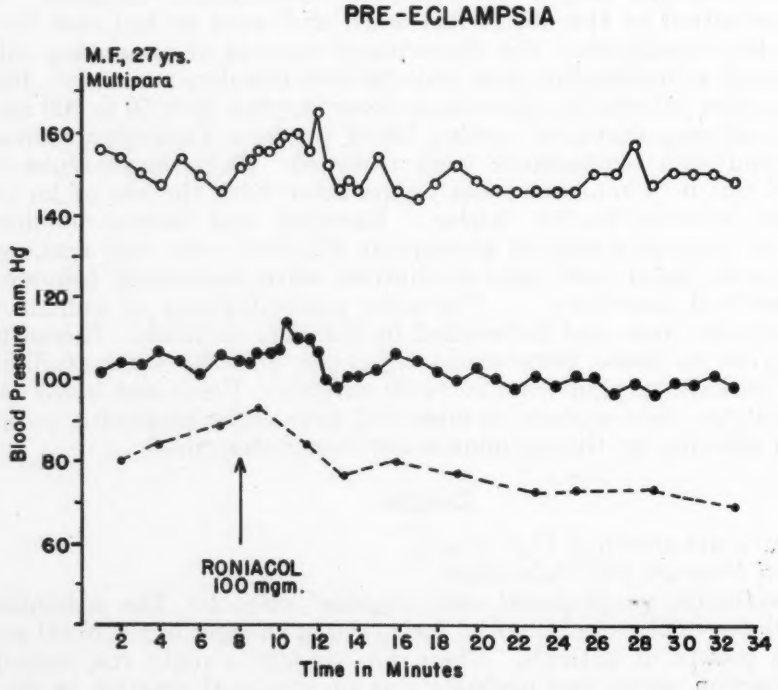

Fig. 2.—The effect of 100 mg. of Roniacol on the blood pressure and pulse rate of a pre-eclamptic patient.

Flushing of the face, neck, and chest occurred in all cases, despite the lack of hypotension. The changes in pulse rate were also insignificant. Postural hypotension was absent.

2. Pre-eclamptic patients: This group also showed inconsistent changes in the blood pressure response to Roniacol. In some instances there was a slight

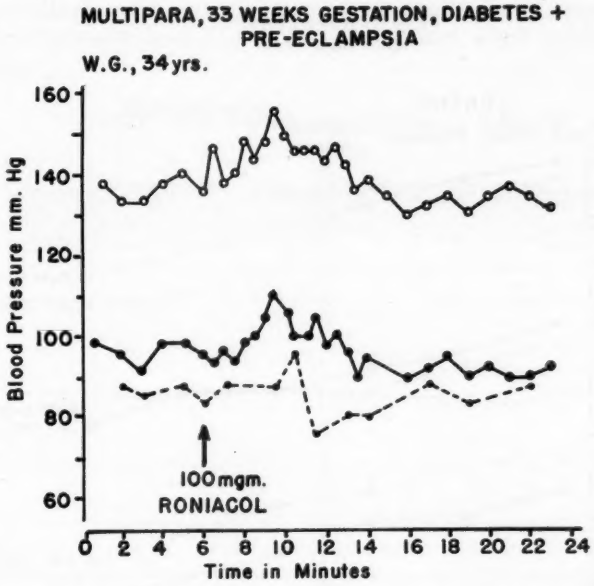

Fig. 3.—The effect of Roniacol on pre-eclampsia associated with diabetes.

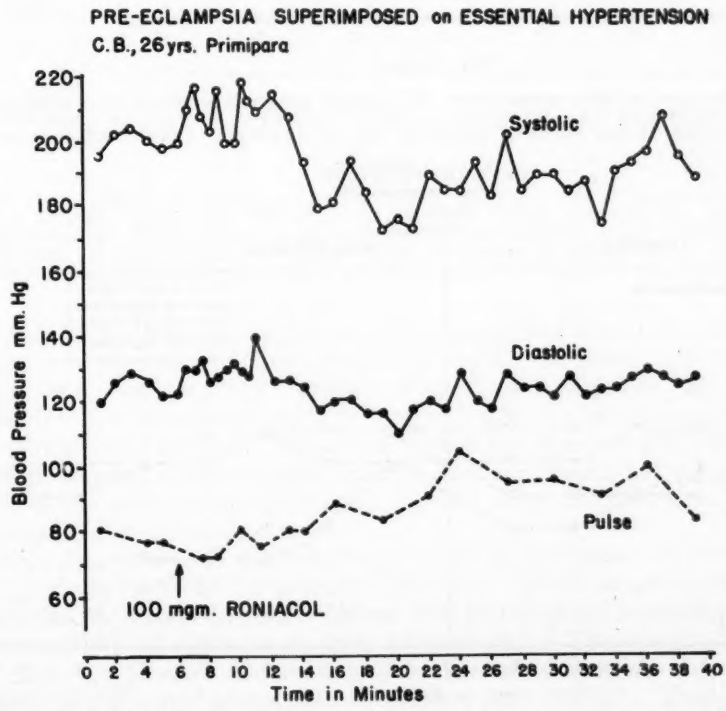

Fig. 4.—The effect of 100 mg. of Roniacol on pre-eclampsia superimposed on essential hypertension.

fall in the blood pressure; in others a slight rise. These changes were considered to be of no statistical significance.

3. Essential hypertension with superimposed toxemia: In this group the hypertension was present before the pregnancy and there was a superimposed toxemia during the last trimester of pregnancy. Roniacol produced no remarkable alterations in the blood pressure or pulse rate of these patients.

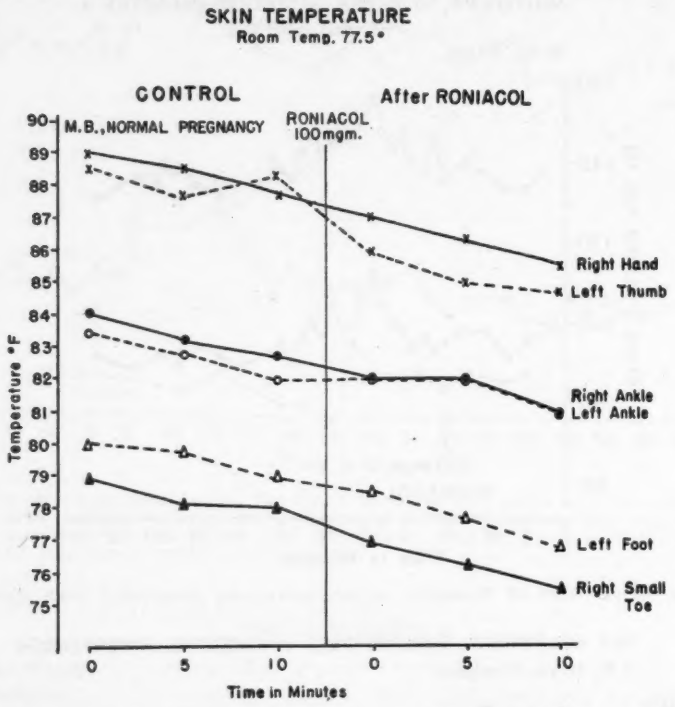

Fig. 5.—Changes in skin temperature of normal pregnancy before and after 100 mg. of Roniacol. This chart and the subsequent one were condensed in order to make them shorter. The downward trend of the curve is probably due to emotional vasoconstriction of the skin.

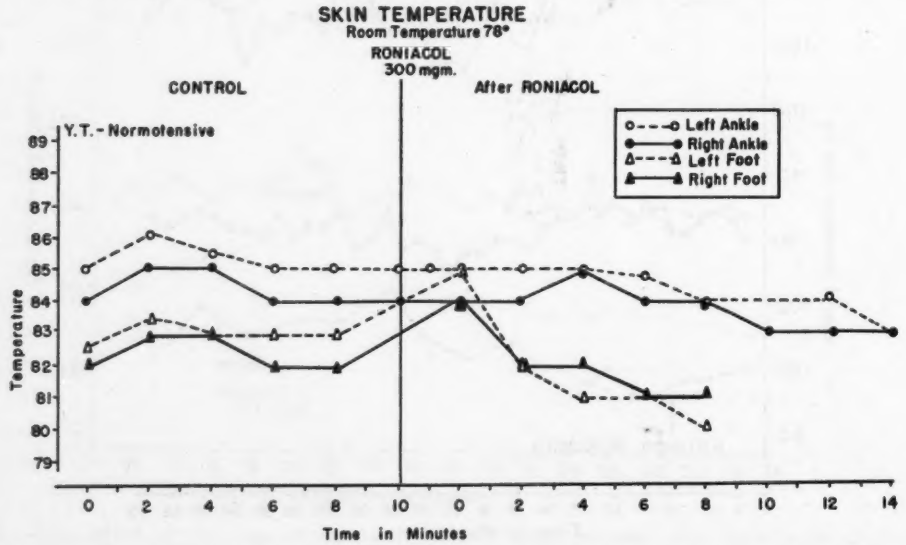

Fig. 6.—This illustrates the effect of 300 mg. of Roniacol on the skin temperature of a well-trained physician. No changes were observed.

B. Skin Temperature.—

Skin temperature was recorded in a room maintained at a constant temperature of 78° F. The patient was lying on a table completely uncovered. A period of one hour was allowed for the patient to adapt to the room temperature. Thereafter, control recordings for approximately 40 minutes were taken from different areas of the body, i.e., the face, neck, chest, upper extremities, abdomen, and lower extremities, particularly the heels, ankles, and toes. The drug was then given intravenously and the same recordings were made for a period of 30 to 40 minutes.

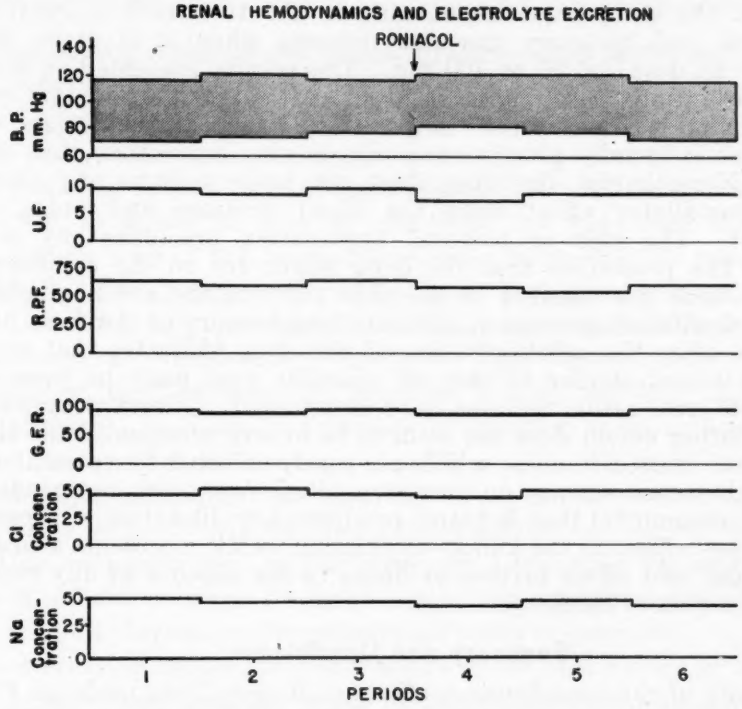

Fig. 7.—The effect of Roniacol on the blood pressure (BP), urine flow (UF), renal plasma flow (RPF), glomerular filtration rate (GFR), and the urinary concentrations of chloride and sodium. This normal pregnant patient was studied under osmotic diuresis with mannitol loading in the hydropenic state. Note the lack of alteration in the renal hemodynamics and the excretion of electrolytes after the administration of the drug.

The results showed no significant changes in the skin temperature of most areas examined except the face, neck, and chest. In these regions there was a rise in the skin temperature varying from 2 to 3 degrees. In the toes and fingers, which are considered of vital importance in the treatment of vascular peripheral disease, the skin temperature changes were negligible. In Figs. 5 and 6 are presented skin temperatures from the extremities, other areas being omitted and the time being shortened for the sake of brevity.

C. Kidney Functions.—

Control clearances of mannitol and para-aminohippurate were performed during 3 periods of 10 to 12 minutes' duration under osmotic diuresis and 25 to 30 minutes of water diuresis. After the intravenous injection of the drug, a similar number of clearances was carried out. The results indicate that Roniacol did not invoke any changes in the minute urine flow (UF), renal plasma flow (RPF), and glomerular filtration rate (GFR). Thus, the filtration fraction remained constant (Fig. 7).

D. Electrolytes.—

Roniacol did not affect the urinary concentration of sodium, potassium, and chlorine. The excretion of these ions remained the same (Fig. 7).

Comment

Experiments carried out on dogs in the Roche Laboratories have shown that the intravenous administration of doses of Roniacol varying from 2.5 to 5 mg. per kilogram of body weight produces a brief reduction in blood pressure. Slightly larger doses invoke active vasodilatation with increased blood flow to the extremities.[8] Clinical observations in man[1, 2] have indicated that the drug is of some value in the treatment of certain types of peripheral and coronary vascular diseases when it is given orally or parenterally in doses of 50 to 100 mg. The results presented in this paper do not substantiate those observations. Although the dosage employed in our patients was not much larger than 5 mg. per kilogram of body weight, which is usually given to animals, it was larger than that employed clinically. Nevertheless, the drug does not seem to have any remarkable arteriolar vasodilator effect since the blood pressure and pulse rate are not changed. The lack of postural hypotension precludes any action on the veins. The possibility that the drug might act on the capillary bed is excluded because the changes in the skin temperature are negligible. The fact that a significant increase in the skin temperature of the face, neck, and chest occurs after the administration of the drug indicates that some local action of Roniacol similar to that of nicotinic acid must be present. The nature of this local action remains to be determined. Clinically, however, this local vasodilating action does not seem to be of any practical value since it is transitory and limited to areas which are rarely affected by vascular diseases.

Although measurements on coronary blood flow were not made in this study, it seems doubtful that Roniacol produces any dilatation of these vessels. The lack of any effect on the kidney circulation which represents a sizable part of the vascular bed offers further evidence to the absence of any remarkable vasodilating action of Roniacol.

Summary and Conclusions

1. A study of the hemodynamic effects of Roniacol was made on 18 normal pregnant women, 12 patients with toxemia of pregnancy, 2 patients with essential hypertension and superimposed toxemia, and 4 normotensive nonpregnant subjects.

2. Roniacol was found to have no effect in these patients on the blood pressure, pulse rate, skin temperature of the extremities, renal circulation, and excretion of electrolytes.

3. Roniacol has a local vasodilator effect on the face, neck, and chest, similar to the action of nicotinic acid.

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VAGINAL HYSTERECTOMY*

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THIS paper is a review of 400 vaginal hysterectomies performed at the Hamilton General Hospital during the five-year period from 1945 to 1949. Of these, 370 were done by the staff of the Department of Obstetrics and Gynaecology and 30 by 8 general surgeons. In the same period of time 180 vaginal hysterectomies were done at St. Joseph's Hospital by the same surgeons. From Jan. 1, 1950, to March 31, 1951, an additional 304 were done at the two hospitals making a total of 884, with one operative death, or 0.113 per cent.

Werner[1, 2] has described the vagina as a "God-given passage to the pelvic organs." Are we, as gynecologists, making proper use of this fortunate anatomical structure? Incidentally, familiarity with vaginal surgery is the really distinguishing mark between the members of such Societies as this and the general surgeon. In order to maintain our position as specialists in a rather restricted field, we must be able to handle pelvic pathologic conditions with safer and better techniques than they do. If we can do this, which the authors firmly believe, not only will we justify our specialty but we will be benefactors to countless women in need of pelvic surgery. It is with the hope of stimulating our members to more frequent use of the vaginal approach to a wide variety of gynecological problems that this paper is presented.

The increasing number of publications in the past decade or so relating to vaginal hysterectomy and the repair of pelvic floor relaxations indicates a revival of interest in the vaginal attack on pelvic disease. We have reviewed the current literature and now present certain trends and conclusions which we believe are supported by our own experience.

In an editorial on vaginal hysterectomy in *Surgery, Gynecology and Obstetrics,* July, 1949, Heaney,[3] the chief advocate of the wider use of vaginal hysterectomy on this continent, said, "When at the end of the last century aseptic surgery became perfected, the abdomen was entered with comparative safety. Gynecologists laregly deserted the vaginal attack on pelvic disease, . . ." He goes on to say, "In most clinics vaginal hysterectomy was abandoned entirely and a generation of gynecologists grew up totally unacquainted with the vaginal approach to pelvic disease."

In advocating the more frequent use of the vagina as a pathway to pelvic pathology, we will first discuss the contraindications to such a procedure. No one would advise the vaginal route to a pelvis filled with chronic inflammatory disease, endometriosis, or large abdominal tumors, especially if fixed, or when their exact pathology is doubtful; nor to most cases of uterine malignancy. In

*Read at the Seventh Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, The Seigniory Club, Montebello, P.Q., June 16-18, 1951.

patients known to have had previous abdominal surgery a vaginal approach must be very carefully weighed, but it should be recognized that even extensive pelvic operations do not necessarily prevent comparatively easy removal of the uterus from below.[4-8] The chief contraindication to a vaginal removal of the uterus is a cervix so fixed that the uterine vessels cannot be ligated satisfactorily. Often this type of uterus is also very difficult to remove abdominally.

The chief objection to the vaginal removal of diseased female reproductive organs is the supposed difficulty of adequate exposure, due to the limited space available. This difficulty can be eliminated very largely by some technique, such as Heaney's, which disposes of obstructing clamps. By his method it is possible to see exactly what one is doing; the placing of clamps is greatly aided by his narrow vaginal retractors and the suturing is made comparatively easy by his curved needle holder. The successful use of this technique was well demonstrated by Campbell's[4] report in 1946 of 2,798 vaginal hysterectomies with a mortality of 0.214 per cent. We do not intend to give any details of his technique, although we use it, because it has already been well described[9, 31] and one of our own members, Dr. H. B. Atlee, gave an excellent description at the last meeting of the Royal College of Canada.

TABLE I. MORTALITY OF VAGINAL HYSTERECTOMY

AUTHOR	NO. CASES	NO. DEATHS	PER CENT
Campbell, Z. B.[4]	7,280*	24	0.32
Eastman, O. N.[8]	1,000	7	
Edwards, E. A.[7]	570	1	
Harrison, J. E.[11]	77	0	
Veenboer, W. H.[17]	104	0	
Cadenhead, E. F.[16]	212	0	
Weir, W. C.[32]	179	3	
Ricci, J. V.[12]	500	1	
Chapman, C.[20]	49	0	
Atlee, H. B.[15]	834	4	
Burke, F. J.[26]	585	3	
Leventhal, M. L.[6]	300	0	
Carter, B.[33]	1,065	2	
Rutherford, R. N.[34]	300	0	
Weaver, R. T.	884	1	
Total	13,939	46	0.31

*Collected from the literature by Campbell, including his own 2,798 cases.

We feel safe in saying that it is now accepted practice among gynecologists, but not among general surgeons, to remove the cervix when doing an abdominal hysterectomy. In other words, most gynecologists now think of a subtotal hysterectomy as an "incomplete operation," only justified under some unusual circumstances. This opinion has been reached after many years of argument and controversy about the relative merit of the two procedures. This controversy has now been replaced in gynecological thinking by one question; whether one should remove the uterus and the cervix by the abdominal route or through the vagina. The authors believe that vaginal hysterectomy, with plastic surgery when indicated, will most frequently eliminate all the pelvic pathology while maintaining a lower mortality rate.

Such a statement could not be made were there not many reports in the literature,[4, 5, 7, 8, 10-17] including our own, showing a mortality rate of well under 1 per cent. Table I shows a collection from the literature of 13,939 vaginal hysterectomies with a mortality of 0.31 per cent. When one adds to this the elimination of future uterine carcinoma, of abnormal nonmalignant uterine bleeding, of ovarian pathologic conditions to a considerable extent, as well as relief of the very annoying symptoms of pelvic relaxations, it seems reasonable

to encourage a more general use of vaginal hysterectomy with colporrhaphy when necessary.

Besides the well-recognized fact of lowered mortality as compared with total abdominal hysterectomy, what advantages are there to a vaginal removal of the uterus? Many authors testify to a decreased incidence of operative shock, of embolism, of bladder and ureteral injuries, of abdominal distention and obstruction of the intestinal tract, and of course, to the complete absence of wound disruption and postoperative incisional hernia.[3, 4, 6, 7, 10, 13, 16, 18-21]

There are three broad groups of patients in whom vaginal hysterectomy, together with any necessary pelvic floor repairs, should be considered the operation of choice. Obviously each patient must be studied as an individual; not all of any group can or should be treated by this method and a very few may need a combined operation.

1. Uterine pathology requiring hysterectomy associated with pelvic floor relaxations.
2. Pelvic floor relaxations requiring surgical correction without known uterine or adnexal pathology.
3. Uterine pathology requiring removal and not associated with pelvic floor relaxations.

When assessing for operation any patient in one of these groups, the surgeon should think first of the vaginal approach; he should decide on the abdominal route or an "incomplete" vaginal operation only for very good reasons. Unfamiliarity with vaginal hysterectomy, except for gross prolapse, may seem like a good reason. However, a specialist in gynecology who is quite competent to do a difficult total abdominal hysterectomy in an obese patient is equally competent to extend his scope in the vaginal approach if he wishes to do so.

The oportunities to perfect ourselves in an adaptable technique of vaginal hysterectomy come to all of us and deserve practice. Quoting Heaney again,[3] "It is interesting to note how those who persist in perfecting themselves in the technique of vaginal hysterectomy gradually disregard more and more of the contraindications so insistently laid down by those with little or no familiarity with the operation." Other authors[4, 6, 7, 10, 14, 15, 19] have stressed this important point.

Holding no brief for surgical gymnastics, such as the removal of huge fibroids through the vagina, we feel very strongly that many difficult total hysterectomies by the abdominal route are less difficult, and consequently more safe, when dealt with from below. This is particularly true in the obese, the cardiac, the diabetic, and the elderly; in fact, most poor surgical risk patients will withstand a vaginal removal of the uterus more safely than they will a laparotomy.[4-8, 10, 15, 16, 22, 23, 24] The amount and duration of anesthesia are usually much less than are required in opening the abdomen; our anesthetists prefer the vaginal to the abdominal approach in those women who present an anesthetic problem.

In our first group, uterine pathology with relaxations, many clinics still resort to a combined vaginal and abdominal procedure, with all the added risks of invading the abdomen and the prolongation of operative and anesthetic time; or two operations are performed a short time apart.

In our second group, pelvic floor relaxations without other demonstrable pathology, it seems rational at first sight to do some form of operation like the Manchester. The authors feel that any operation to relieve the symptoms due to damaged supports which leaves the body of the uterus (Manchester, Watkins, LeFort), or a portion of the cervix (Spalding-Richardson), or fails to give the opportunity to inspect, and when necessary remove, the adnexa, must be considered an "incomplete operation." Such procedures are quite

proper under special, but very infrequent, circumstances; for example, a Manchester in a young woman requiring repair who has not completed her childbearing function.

Shaw's[25] most interesting and convincing article in 1933 did much to prove that prolapsus uteri can be cured by an adequate repair and has encouraged untold numbers of "incomplete operations" throughout the world. It is unfortunate that he did not give us some information in his follow-up of the number who later developed carcinoma of the uterus, nonmalignant uterine bleeding requiring surgical treatment, and ovarian pathology which might have been eliminated by a complete operation in the first place without increasing the primary mortality rate. A trend toward vaginal hysterectomy can be discerned even in the British Isles where the Manchester had its origin.[26, 27]

In our third group, uterine pathology requiring hysterectomy but without relaxations, most of us naturally think of the abdominal route. However, it is in this group that the most spectacular successes of vaginal hysterectomy occur. In many the operation is surprisingly easy,[3, 4, 5, 10, 18, 19] and the postoperative course often resembles that of some minor procedure.

Most of the discomfort and morbidity associated with vaginal hysterectomy are actually due to the extensive dissection of the vaginal walls. In many nulliparous and even virgin women, a uterus can be removed through the vagina more quickly and with less difficulty than through the abdomen. As there is no repair, there is less postoperative discomfort and the avoidance of an abdominal incision eliminates a number of possible complications.

Table II shows the hysterectomies of all types performed at the Hamilton General Hospital from Jan. 1, 1945, to March 31, 1951. It will be noted that the percentage of vaginal hysterectomy to abdominal has risen from 27.4 to 38.7. This table also shows that the incidence of incomplete hysterectomies has fallen from 6.0 to 2.2 per cent.

We have reviewed the vaginal hysterectomies performed at the Hamilton General Hospital for a five-year period from 1945 to 1949, a total of 400 cases with one death. This period of time was chosen in order to have over a year's follow-up, in the belief that the majority of recurrences of gynecological pathology will show some evidence in that time.

TABLE II. ALL HYSTERECTOMIES, HAMILTON GENERAL HOSPITAL

	ALL HYST.	TOTAL ABDOMINAL	VAGINAL HYST.	PER CENT VAGINAL TO ABDOMINAL	SUBTOTAL	PER CENT SUBTOTAL
Jan. 1, 1945, to Dec. 31, 1949	1,543	1,049	400	27.4	94	6.0
Jan. 1, 1950, to March 31, 1951	412	246	157	38.7	9	2.2
Total	1,955	1,295	557	30.0	103	5.3

None of us had special training in vaginal surgery but by assisting each other we were able to build up our confidence and proficiency. As has already been mentioned, increasing familiarity with the vaginal approach widens its usefulness.

Of the 400 patients only 32, or 8 per cent, have not been traced; reasonably reliable reports have been obtained on all the others. All have been examined by a physician; in the vast majority by the surgeon as well as the family doctor. There have been 14, or 3.5 per cent, who required reoperation for some form of pelvic floor relaxation. There are about an equal number, many free of symptoms. who have relaxations at present insufficient to warrant further

surgery but who may come to operation at a later date. It is quite possible, too, that some of those untraced may have been reoperated upon elsewhere, but we think it is safe to say that over 90 per cent have had satisfactory anatomic results. In the period under review very few nulliparous women are included; at least 98 per cent had varying degrees of prolapse.

In this connection the authors wish to draw attention to the much-quoted report of Everett[28] in 1935. In 1943 Te Linde[29] quotes him to this effect: "Everett also found that in 30 per cent of the women upon whom a vaginal hysterectomy was done there was an unsatisfactory anatomic result." In his textbook, *Operative Gynecology,* July, 1946,[30] he makes essentially the same quotation from Everett. This opinion from a gynecologist of the prominence that Te Linde so rightly deserves, and from a medical school with the world-wide reputation of Johns Hopkins, carries immense weight with the profession. It is almost impossible to believe that Everett's[28] original report dealt with 26 vaginal hysterectomies with a follow-up on 17! Yet it has doubtless discouraged many surgeons from utilizing this valuable procedure. Should an opinion based on such figures be compared in real value with those of Green-Armytage,[27] and many others, based on thousands of cases?

Three ovarian malignancies were found at operation and removed; all these patients died between two and three years later as a result of carcinoma. All were over the age of sixty and had marked prolapse of the uterus. In two an ovarian tumor was recognized before the operation, complicating the prolapse, one was 7.5 cm. in diameter, the other 8. In the third case the ovary was normal in size but was adherent to the broad ligament and numerous small nodules were observed on the peritoneum and bowel.

Two of these received x-ray therapy within a few days of their operations, while the third had palliative treatment for secondary metastases. There seems no reason to believe that the type of operation contributed at all to the final result.

Previous abdominal surgery is often quoted as an absolute contraindication to vaginal hysterectomy. In our series the number of patients with previous pelvic surgery, excluding dilatation of the cervix and curettage of the uterus, was 26, as shown by the hospital records, probably considerably less than the actual figure. Many others had had previous upper abdominal surgery and intestinal operations, the most common being appendectomy. Of the gynecological cases, 7 had had suspensions, 6 had had vaginal plastic procedures, and the others covered the field of surgery on the uterus and adnexa. Although adhesions of various kinds were encountered at times, they rarely offered any serious operative difficulty.

Any total extirpation of the uterus carries with it some risk of injury to the bladder, the ureters, and the bowel. It is unfair to compare a series of total abdominal hysterectomies with an equal number of vaginal hysterectomies, because of the fact that those patients most liable to such accidents will usually be operated on by the abdominal route even in those clinics which favor the vaginal approach whenever possible. However, many gynecologists specially fear these injuries when operating through the vagina, a fear which seems unjustified by the reports in the literature. In our series there were no injuries to the bladder or the ureters. The urethra was opened once and healed without difficulty. The rectum was opened twice; one case resulted in a recto-vaginal fistula which was successfully repaired about a year later. One patient required laparotomy nine days postoperatively for a small-bowel obstruction, an extremely unusual complication in vaginal hysterectomy.

The one death distresses us considerably, as we feel it must be called a preventable death. The patient died from massive pulmonary embolism on the tenth postoperative day after getting dressed to go home. She had a marked

degree of prolapse for which a vaginal hysterectomy was performed without difficulty, followed by an uneventful postoperative course. We believe her death was due to an error in judgment in failing to employ anticoagulants with her operation, for she had required them for an acute phlebitis following the birth of her last child about six months before. However, embolism is not a common hazard in this type of surgery.

Summary

Four hundred consecutive cases of vaginal hysterectomy have been reviewed and a total of eight hundred eighty-four reported with one operative death.

The current literature has been studied and we believe demonstrates an increasing use of the vaginal approach to pelvic pathology in the English-speaking world.

In 13,939 vaginal hysterectomies collected from the literature there was a mortality rate of 0.31 per cent.

The contraindications and operative difficulties have been much exaggerated by the infrequent vaginal operator.

By increased familiarity through cooperative effort any gynecological staff will find its enthusiasm for the procedure growing and its scope widening.

In the treatment of uterine prolapse, a vaginal repair without removal of the uterus and cervix is an "incomplete operation" and rarely justified.

Vaginal hysterectomy, with suitable repair, is usually the best treatment for prolapse of the uterus.

Many diseased uteri should be removed through the vagina even when no repair is necessary.

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MEDICAL ARTS BUILDING

SUPPRESSION OF LACTATION WITH STILBESTROL

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ENGORGEMENT of the breasts and lactation in the nonnursing mother can be a source of much discomfort and annoyance in an otherwise relaxed and enjoyable puerperium. The prevention of these developments and the symptoms which arise therefrom can add greatly to the mother's restfulness while in the hospital and can remove at least one source of difficulty from the many which beset the new mother at home. Numerous reports have appeared in the literature regarding the use of estrogens for the suppression of lactation. However, the results which have been reported have not been uniform.

The rationale of this therapy is not clearly understood. Presumably, under normal circumstances, with the delivery of the fetus and placenta, there is a marked reduction in the titer of circulating estrogen in the maternal circulation resulting in a release of inhibition of the anterior pituitary gland which then secretes the lactogenic hormone, which in turn initiates lactation. The presumption is that if the lactogenic function of the anterior pituitary gland could be suppressed for a period of time, while the breasts are kept from exposure to the stimulating action of suckling, lactation would not occur. Theoretically, such artificial inhibition of the anterior pituitary gland might be accomplished by means of an estrogen or an androgen, and, indeed, both agents have been tried.

An exhaustive review of the literature would be needlessly repetitious. A few of the reports appearing in recent years regarding the use of estrogens for this purpose are summarized in Table I.

In contrast with these results Gershenfeld and Perlmutter,[9] using ethinyl estradiol in daily doses of 1.5 mg., found that 34 per cent of patients had pain and 26 per cent had engorgement, and that after leaving the hospital 43 per cent of patients had pain, 46 per cent engorgement, and 60 per cent, lactation. Lubin,[10] likewise using stilbestrol in relatively large doses in 50 patients, noted engorgement in 50 per cent of his patients, pain in 12 per cent, and colostrum or milk in 80 to 90 per cent. In his 50 controls, 80 per cent had engorgement and 42 per cent pain, but only 12 per cent had enough discomfort to require medication for relief. He noted a sharp increase in lochia rubra in patients receiving stilbestrol and concluded that the routine use of the drug was inadvisable. Rakoff and co-workers[1] found that established lactation promptly subsided on dienestrol; Kurzrok and associates[5] reported a similar experience with ethinyl estradiol. Douglas and Wanless,[2] on the other hand, found that stilbestrol in 15 mg. doses was not efficacious in suppressing established lactation.

Despite the fact that the majority of reports indicate a relatively great degree of success in the suppression of lactation by means of an estrogen, many of us who have tried it rather casually have had reasons to doubt its advisability.

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Our doubts have arisen because of failure of the method in many instances, because our patients have often gone home after seemingly successful suppression in the hospital only to have engorgement and uncomfortable filling of the breasts occur at this later time, and because in some instances it has seemed that these patients have experienced more puerperal bleeding than was expected or was desirable. We have also been disappointed in the results when an estrogen has been given to suppress already established lactation, a procedure which has become rather common practice. The present study was carried out in an attempt to clarify the discrepancies in the reported results and the uncertainties expressed above. It was felt that the following questions needed answering:

1. Does an estrogen, such as stilbestrol, if given during the puerperium, actually suppress lactation?
2. What relation has time of starting the therapy upon the outcome?
3. What part do dosage and duration of treatment play in the success or failure of the method?

TABLE I

AUTHOR	NO. OF PATIENTS	DRUG	AMOUNT	RESULTS
Rakoff et al.[1]	26	Dienestrol	6.5 mg. in 10 days	Entirely satisfactory
Douglas and Wanless[2]	18	Stilbestrol	10 mg. daily	Satisfactory
Birnberg et al.[3]	145	Ethinyl estradiol	1.5 mg. in 9 days	58 per cent excellent 16 per cent good
Abarbanel and Goodfriend[4]	65	Stilbestrol	30-40 mg. in 4-5 days	38.5 per cent excellent 47.7 per cent good
Kurzrok et al.[5]	16	Ethinyl estradiol	1.35-2.4 mg. daily for 2-3 days	75 per cent satisfactory
	26	Ethinyl estradiol	0.45-0.9 mg. daily for 3 days	65.4 per cent satisfactory
Dunlap and Diddle[6]	95	Stilbestrol	5-10 mg. daily for 7 days	90 per cent good or fair
	61	Alpha estradiol	0.5-2.5 mg. daily for 4 days	77 per cent good or fair
	125	Dienestrol	1.5-1.8 mg. daily for 3-9 days	90 per cent good or fair
Barnes[7]	81	Stilbestrol	30 mg. in 5-7 days	60.5 per cent satisfactory
	37	Dienestrol	3-5 mg. in 5-7 days	40.5 per cent satisfactory
	16	Hexestrol	30 mg. in 5-7 days	37.5 per cent satisfactory
Hanley[8]	153	Stilbestrol dipropionate	8-16 mg.	67.8 per cent satisfactory

Material and Methods

The 252 patients used in this study were taken from the private practice of the senior author at the University of California Hospital and from the ward patients at the San Francisco Hospital and St. Luke's Hospital, San Francisco. The observations during the patients' hospital stay were made and recorded by us daily except in a few instances where they were taken from the hospital charts of the University of California Hospital. The follow-up observations were made by telephone, by letter, and by observations in the outpatient department. Diethylstilbestrol was the drug used throughout the study.

Seven groups of patients were studied:

a. Seventy-three patients were given stilbestrol, 1 mg. daily, starting within 24 hours of delivery and continued an average of 7 days.

b. Sixty-one patients were given stilbestrol, 5 mg. daily, in the same manner as above.

TABLE II

DAILY DOSE STILBESTROL	NO. OF PATIENTS	METHOD	RESULTS			
			SATISFACTORY INITIAL (HOSPITAL) RESULT	INITIAL (HOSPITAL) FAILURE	UNSATISFACTORY LATE RESULT	COMPLETELY SATISFACTORY RESULT, NO FILLING EARLY OR LATER
(a) 1 mg.	73	Started within 24 hours after delivery, continued during hospital stay	55	18	No observation	
(b) 5 mg.	61	Started within 24 hours after delivery, continued during hospital stay	55	6	No observation	
(c) 5 mg.	21	Started within 24 hours after delivery, continued during hospital stay	18	3	12	6
(d) 5-10 mg.	60	Same as (a) and continued in diminishing doses at home for 1 month	57	3	1	56 (93.4%)*
(e) 5-10 mg.	9	Start of medication delayed 40-72 hours	1	8	0	1
(f) 15 mg.	10	Nursing discontinued and medication started after 72 hours	4	6	0	4
(g) Controls	18	No medication	3	15	–	–

*Fourteen of the 60 patients in (d) had slight postpartum bleeding not definitely attributable to stilbestrol, and requiring no treatment.

c. Twenty-one patients were given stilbestrol, 5 mg. daily, in the same manner as above and careful follow-up was obtained for at least 2 weeks after discharge from the hospital.

d. Sixty patients were given an initial dose of 5 to 10 mg. stilbestrol, then 5 mg. daily for 7 to 10 days, and were then sent home with 40 1-mg. tablets with instructions to take 4 tablets daily for 4 days, 3 for 3 days, 2 for 2 days, then 1 daily until the tablets were gone.

e. Nine patients were given stilbestrol, 5 to 10 mg. daily, starting between 40 and 72 hours of delivery and continued for 3 to 4 days.

f. Ten patients who discontinued nursing after 3 days were given stilbestrol, 15 mg. daily, from the third to seventh day post partum.

g. Eighteen patients who did not nurse were given no medication.

Results

The results are shown in Table II.

The result was considered satisfactory if no engorgement or pain or tenderness occurred, or if only minimal discomfort occurred which lasted not more than two days. The same criteria were used in judging the results after patients had left the hospital, although in most cases the patients' subjective reaction had to be depended upon more fully.

Comment

The results show clearly that stilbestrol inhibits breast engorgement, lactation, and tenderness in approximately 90 per cent of nonnursing mothers, provided that the medication is started within 24 hours after delivery, and that it is continued for a long enough period of time after the patient has left the hospital. The exact minimum period during which stilbestrol therapy should be continued to achieve permanent suppression we do not know. The four weeks' period suggested itself to us because of the not infrequent observation of filling and leakage as late as three weeks post partum when the drug had been stopped before this time. We have not noted this difficulty when the drug was given for four weeks. A daily 5-mg. dose appeared to be adequate in 90 per cent of patients. We have noted occasional failures on doses as large as 15 or 30 mg. daily and other observers have reported similar incidences of failure on the larger doses.

The results indicate that it is most important that treatment be started immediately after delivery. On the other hand, if it is not started within 24 hours it may as well be withheld altogether for in our experience stilbestrol is of little or no value in suppressing lactation and engorgement once these have become manifest. This is likewise true in the mother who starts to nurse and then stops, as is shown in Group f above. In 6 out of 10 mothers it required over 48 hours for breast signs and symptoms to regress, a result no better than that obtained when no medication is used.

Some have stated that estrogens used to suppress lactation cause an increase in lochia and in postpartum bleeding. Of the 60 patients to whom we gave stilbestrol over a prolonged period of time 14 reported "some undue bleeding" at one time or another. In none of these was the bleeding significant enough to require treatment and in none could a relationship with the stilbestrol therapy or its withdrawal be established. The uterus of the nonnursing mother rarely involutes as rapidly as does that of the nursing mother and it would seem difficult to incriminate stilbestrol per se as the cause of any increased lochia or bleeding in the puerperium. In our series there was no case of significant postpartum bleeding which could be attributed to stilbestrol.

It has been said that suppression of lactation with estrogens is unnecessary because breast engorgement rarely causes enough discomfort to require relief. Our experience has been by no means this fortunate. We would agree that the tender, engorged, leaky breast is rarely if ever a serious puerperal complication; nevertheless stilbestrol when properly used offers a safe, rational, and effective means of preventing symptoms which may interfere considerably with the comfort and rest of the puerperal woman.

Summary and Conclusion

1. Stilbestrol was given to 234 mothers in varying doses and dosage schedules for the purpose of determining its value as an agent for the inhibition or suppression of breast engorgement and lactation.

2. A daily dose of 1 mg. of stilbestrol inhibited signs and symptoms of lactation in 75.3 per cent of patients while they were in the hospital. A daily dose of 5 mg. inhibited signs and symptoms in 85 to 93 per cent of patients during their hospital stay.

3. Stilbestrol therapy is of little or no value in suppressing lactation once it has become established.

4. To achieve the maximum possibilities of the treatment, the drug must be started within 24 hours after delivery.

5. Treatment must be continued for a longer period than the usual hospital stay to prevent late engorgement and lactation. A gradually diminishing dosage schedule is presented which in our experience has been safe and simple to follow and which has given satisfactory results in 93.4 per cent of patients.

6. In this series there was no case of postpartum bleeding which was thought to be attributable to stilbestrol.

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INTRAVENOUS PROCAINE-PENTOTHAL DURING LABOR

Preliminary Report

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THE intravenous administration of a dilute solution of procaine has been widely used as a means of pain relief in a variety of conditions. These have been summarized by Grabaurd and Peterson,[1] who have been leading exponents of its use.

It is only natural that in the search for an ideal analgesic for labor this drug should be considered. Allen[2] studied its effects in a series of maternity cases and stated he obtained good results. The convulsions which occasionally occur with his technique are easily controlled with intravenous Pentothal Sodium. Johnson and Gilbert[3] also reported good results with the use of procaine during labor. The studies of Frazer[4] with a dilute mixture of procaine and Pentothal as an adjunct to surgical anesthesia seemed to us to point in the proper direction. He used this mixture in varying concentrations to produce anesthesia either alone or in combination with other anesthetic agents. We decided to study the value of this mixture of procaine and Pentothal Sodium as an analgesic agent during labor.

Procedure

Pentothal Sodium and procaine hydrochloride in 0.1 per cent solution each in saline are incompatible. The reaction is slow as shown by the passage of 6 to 10 hours before the crystals start to precipitate out visibly. Since the solution is administered in 2 to 3 hours, we decided to ignore the incompatibility and use it as such. Consequently, our mixture was prepared by adding 1 Gm. of Pentothal Sodium to 1,000 c.c. of the commercially available 0.1 per cent procaine* solution. This was prepared fresh for each patient immediately prior to administration. A 20-gauge needle was inserted into a vein of the antecubital fossa or into one of the veins of the forearm. The forearm is preferable since it allows the patient some motion of the arm without fear of dislodging the needle. The arm must be tied to a board if the antecubital space is used. The solution is allowed to run in at will, usually about 150 drops per minute, for 20 to 30 minutes and then is slowed to 75 to 100 drops per minute. Thus a liter of solution is administered in two to three hours.

The patient is watched, either by an anesthetist or one of the obstetrical nurses, for untoward symptoms such as nausea or dizziness. The pulse and blood pressure are watched to note any untoward change. At the same time close watch is maintained on the fetal heart rate. The only treatment necessary for any of these complications, should they occur, is the slowing of the rate of administration. Thus far we have had no undesirable reactions.

*The 0.1 per cent procaine solution used in this study was generously supplied by the Abbott Laboratories.

When the patient is nearly ready for delivery atropine, 1/150 grain, should be given intravenously into the tubing of the intravenous set to prepare the patient for the administration of a general anesthetic, should this be necessary. With the usual analgesic methods where scopolamine is freely used the secretions are well dried up and preanesthetic administration of atropine is unnecessary. With this technique to avoid an unpleasant general anesthesia its use should not be forgotten.

Results

There were 8 primiparas in the group; 7 multiparas having their second babies; and 10 multiparas having their third to eighth babies. The patents varied in age from 18 to 36 years.

At the time of the start of the analgesia, dilatation of the cervix varied from 3 to 5 cm. The pains at this time were coming 3 to 5 minutes apart and were of good quality.

The average dose of the combination was about 900 c.c., with a minimum of 300 c.c. and a maximum of 1,200 c.c. This was given in from 30 minutes to 4 hours with average length of administration about 2 hours.

Nearly all these patients were delivered under gas, oxygen, ether anesthesia. Two had no additional anesthesia and one a saddle block. There were 7 low-forceps deliveries, 17 spontaneous, and 1 breech. The perineum was intact in 14 cases, while in the other 11 cases medial episiotomies were done.

Comment

Excellent results were obtained with this method of analgesia. Some trial-and-error experience was necessary to determine the optimum rate of administration, which is still varied with the individual patient. The basis from which to vary is described under "Procedure."

No instances of undesirable side effects were noted. There were no complaints or toxic symptoms which might in any way be attributable to the drug combination.

Good analgesia was obtained in all cases. The patients usually felt sleepy; some dozed most of the time, waking to state they had a contraction but that it didn't bother them particularly.

The desired effect with this analgesic technique is to reduce the intensity of the pain stimulus by means of the procaine and at the same time produce mild sedation with the Pentothal. The patients feel relaxed and sleepy. In several instances amnesia was produced, but we feel that this was an incidental finding, in contrast to those analgesic methods whose primary aim is the production of amnesia.

There was little, if any, depressant effect on the babies. All babies cried spontaneously immediately after birth, frequently before being completely delivered; resuscitative measures were not necessary. This was in marked contrast to those patients who had analgesia with barbiturates and synthetic opiate derivatives.

Although unable to substantiate our impression statistically, it seems that labor progressed more rapidly with this than with the other analgesic methods. The patients themselves frequently commented that with the medication their contractions seemed to increase in frequency and intensity although they did not mind them so much. There was no interference with the bearing-down sensation and the patients readily pushed and hastened the expulsion of the fetus. They were all completely oriented and able to cooperate, which is again in contrast to the usual technique.

Conclusions

The chief disadvantage we have found is the fact that the patients must be observed closely throughout labor, so that the use of this analgesic method may be restricted by lack of adequately trained personnel.

There are several outstanding advantages. The patients remain oriented and able to cooperate, and depressant effects on the babies are absent. In contrast to the ordinary analgesic routines, the depth of analgesia may be controlled so that the needs of each individual patient may be met according to the intensity of labor.

The intravenous administration of a procaine-Pentothal mixture is a valuable analgesic during labor when used in the described fashion. It seems to be safe for both mother and baby in our small series of twenty-five cases. Further investigation will determine fully its value.

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Special Article

THE MATERNAL MORTALITY REMAINDER*

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THE United States is the first great nation to breach the wall of one maternal death per 1,000 live births. The National Office of Vital Statistics[1] believes that the maternal mortality rate for 1949 will be nearly 20 per cent lower than for 1948 and estimates it as 8.2 per 10,000 live births and not as 0.8 per 1,000. This statistical innovation no doubt has its advantages, yet it fails to dramatize the startling decline to a new low which many have called the irreducible or inescapable minimum. For the first time the patient may be told that her chances of surviving pregnancy are better than 999 in 1,000 and getting better every year. It should be kept in mind too that this includes the considerable risk of ectopic pregnancy and abortion. There is, however, a wide racial differential in that the rate for the non-white races is more than three times as high as the rate for white women.

From 1915 to 1929 the national maternal mortality rates[2] remained at about the same level with the exception of the high points of 1918 (9.2) and 1920 (8.0). From 1930 to 1936 steady but little improvement occurred. Since then the rate has speedily decreased. In 1948,[2] the last year for which complete data are available, the number of maternal deaths was 4,122 and the mortality rate 1.2 per 1,000 live births. That year there were 3,535,068 live births or but 4.5 per cent less than the all-time high figure of 1947, or nearly one and one-half million more than in 1933 when the maternal mortality rate was more than five times as high.

It is now said[3] that "the maternal death rate is no longer a serious national problem, but rather one for local action in those areas in which rates are relatively high." It will always remain a local problem, and not only where rates are high. In Brooklyn, for instance, where the rate has been below 1 since 1946, it is not a hazardous prediction to say that it will continue to decrease. It is not easy to figure a time scheme for further reduction, but it can be reduced.

The greatest number of maternal deaths ever recorded in the United States was in 1928 when 44 states reported 15,461 deaths. Interest in the comparability of national statistics was high shortly before 1930. The Children's Bureau compiled a table[4] in which the maternal mortality rate of the United States from 1926 to 1928 exceeded that of any other country on the list. It was higher than in Australia, England and Wales, Ireland, Italy, Japan, New

*Read before the Medical Society of the County of Kings, May 15, 1951.

Zealand, Scotland and Sweden. The low rate in the Scandinavian countries and in Holland, though not fully explained, was attributed to the great attention paid to the training and status of midwives in those countries. Haven Emerson[5] maintained that "international comparisons based on national maternal mortality were misleading." In another Children's Bureau[6] publication Tandy showed that the rates were directly comparable. As recently as 1940 controversy was bitter. An editorial in *The Journal of the American Medical Association* said that "maternal mortality rates of the United States have been reported and discussed for several years apparently to conjure conclusions designed to throw discredit upon the medical profession. . . . Again and again the propagandist alleged that the United States was lagging behind most of the other modern nations in its maternal mortality rate. This conclusion was reached by comparing nations some of which were not larger than some counties in the United States, and with an exclusively white population less than that of some American cities, with the entire continental United States with its wide diversity of population including 10 per cent of Negroes with a peculiarly high maternal mortality rate."

In the decade ending in 1930 obstetricians in this country appeared to divide themselves into conservatives and radicals in the management of normal labor.[7] In 1929 Polak,[8] a powerful advocate of natural methods in the conduct of labor, thought that lack of prenatal care, interference with normal labor, and unnecessary cesarean sections contributed to the high maternal mortality, "the result of the teachings of some prominent obstetricians who have been busy inventing operative procedures to control the onset of labor, or shorten or eliminate the second stage of labor or improve the physiologic mechanism of placental delivery. One of these men induces labor in all women at term; another cuts the perineum of every primipara, while still another does a section on every tenth woman and a version on the other nine. Most remarkable of all is the teaching of one of our leading obstetricians who classes all labor as pathologic and advocates rapid delivery with forceps through a cut pelvic floor as soon as the head has passed through the cervix, folllowing this by manual removal of the placenta." In 1931 Adair[9] who, with Holmes and Lynch, had long been active on the Advisory Council of the Children's Bureau and later became chairman of the American Committee on Maternal Welfare, which was incorporated in 1934, said that "the high maternal death rate in this country is a reflection on the training and education of the personnel responsible for furnishing maternity care."

Prior to enactment of the Shepard-Towner Act of 1921, maternal health activities were carried on by but a few State Health Departments or State Medical Societies.[10] Aside from certain writers of the past who had touched in one way or another upon the number of maternal deaths, general medical interest lagged. It is less than twenty years since the shortcomings of American obstetrics were paraded in the public press, and it is much less than that since victory over maternal death statistics was won—if it has been won, yet the impact of the conquest has been so slight that they who have been re-

sponsible for the victory hardly know that there was a battle. The Brooklyn Committee on Maternal Welfare began its work in 1934, shortly after what was called the unnecessary deaths of mothers had become a common topic of discussion in the daily press. In 1933, the preceding year, the maternal mortality rate for Brooklyn was 7 with 284 maternal deaths while the rate for the entire City of New York was 6.4.

The great progress that has been made since that time is largely due, in my opinion, to critical analysis and discussion of our own end results and steady increase in the number of qualified obstetricians. It has long been said that general practice will always carry the heavy burden of obstetrics. That is no longer true.

The history of the great attack on maternal mortality has never been written, though it should be. It is not yet finished, for the maternal mortality remainder is an attractive target. Another generation of obstetricians will need inspiration. To turn aside for a few moments will not be a digression. It is good to look backward, for it will help us to go forward.

As early as 1917, Kosmak,[11] the first crusader, interested the New York Academy of Medicine in a five-year study of puerperal mortality in the hospitals of New York City; nothing was published, however. In 1924 DeNormandie, at the request of the Children's Bureau, formed a committee which drew up standards of prenatal care[12]; and in 1926, as chairman of its Obstetric Advisory Committee, he presented to the Children's Bureau a fine plan[13] for detailed study of the maternal deaths in fifteen states which was published in 1933. In 1930 Lobenstine and Kosmak, as a committee of the New York Obstetrical Society, joined the Children's Welfare Federation of New York City[14] in publication of standards for maternity care. In 1931 the Medical Society of New Jersey[15] appointed a committee on maternal welfare to enlarge the educational program organized in Essex County by Bingham in 1923. Some postgraduate courses in obstetrics, notably by Calkins in Kansas and Oklahoma, and McCord in Georgia round out the medical scene fairly well.[16]

A quotation from the 1930 report of the Committee on Maternal Welfare of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons[16] (Irving W. Potter, Willard R. Cooke, and L. A. Calkins) will help to illustrate the public interest in the problem: "An interesting side light has been thrown several times lately upon the question of maternal welfare by the invasion of this field by the lay woman, through the medium of the popular magazine. One such discussion . . . gives a history of the growth of the use of the Gwathmey method of synergistic analgesia. . . . When one considers the enormous circulation which this magazine enjoys, together with the fact that the author reports some 5,800 cases in which the method has been used in the New York Lying-In Hospital, in which 85 per cent of the patients had almost complete relief from pain, as well as the fact that, after quoting experiences of a similar type from Chicago, Madison, Cincinnati, Pittsburgh and Philadelphia, together with Ottawa and Montreal, she concludes the article with a challenge to women to demand that their obstetricians look into the matter

and see if it is not possible to give them well, live babies after normal deliveries without surgical interference, and practically without pain, one realizes such a woman may have a great deal of influence; good or bad as the case may be." A little later articles in the same journal by de Kruif,[17] under the title, "Why Should Mothers Die?" attracted wide attention.

In 1929 a survey of the hospital and health facilities of Philadelphia conducted by Haven Emerson[18] pointed out that the maternal death rate had been stationary for the previous ten years. The following year the Philadelphia County Medical Society set up a committee on maternal welfare under the direction of Philip F. Williams.[18] This committee, however, decided to follow the line of survey and analysis then in progress by the Committee on Public Health Relations of the New York Academy of Medicine.[11] The New York survey had grown out of recommendations made by Ralph W. Lobenstine and George W. Kosmak. It is generally held, and properly, I believe, that the influence of the New York report has been very great. The Philadelphia report,[18] equally outstanding, was published one year later. By that time the New York report had had tremendous publicity, not all favorable. The New York report emphasized preventability of maternal deaths, the relative safety of delivery at home, expansion of midwife training and opportunity, and said that "the hazards of childbirth in New York City are greater than they need be. Responsibility for reducing them rests with the medical profession."

With publication of the report, the Medical Information Bureau of the Academy of Medicine released an abstract to the daily newspapers under the title, "Why Women Die in Childbirth." A storm of lay and medical criticism followed. The New York Obstetrical Society believed that these newspaper articles had created unnecessarily alarming, misleading, and unfortunate impressions. A committee[19] with Eliot Bishop as chairman commended the entire report but took issue with many phases of it. The report of this committee was printed and given to the daily press.

DeLee[20] said, "Owing to the undiminishing maternal mortality in the United States, voices have been raised demanding the return of the midwife." In Great Britain a debate in which the leaders of British obstetrics and gynecology participated was conducted by the Fellowship of Medicine on the motion, "That the Present High Rate of Maternal Mortality is a Discredit to Modern Obstetrics." No decision was reached, but a verbatim report of the debate was published.[21]

In 1933 a survey of obstetrical facilities was made in Rochester, N. Y., and Quigley,[10] conducting an active campaign there, organized a group for analysis. The county medical societies of New York City soon organized committees following the lead of Philadelphia. In 1935 the maternal death conferences which Skeel[22] had organized in Cleveland in 1932 grew into the Hospital Obstetric Society of Ohio. Boston and the Pacific States conducted their own surveys. States and groups activated committees on maternal welfare and consciousness grew rapidly. This history of the "Great Crusade" is necessarily incomplete, yet I hope there are no major gaps in my record.

Now as if our aim were to reduce the number of maternal deaths statistically rather than actually, we have an ally in the New International Statistical Classification[23] which has been used in New York City since 1949. When multiple causes are mentioned in the certificate of death, the primary cause is no longer tabulated by rule but as stated by the certifying physician, except where the order of entries on the certificate is clearly incorrect. At the moment the exact importance of this change is not known, yet that it will change mortality trends is clear. It has been estimated that puerperal conditions will decline 7 per cent for this reason alone.[24]

In 1950 in the entire City of New York,[25] 112 puerperal deaths occurred. In Brooklyn there were 38. The puerperal death rate per 10,000 reported terminated pregnancies in Brooklyn was 5.4 while for all five boroughs of the City it was 5.6. The non-white rate however was three times as high as the rate for white women. This extraordinarily low maternal death date for a great city with a large non-white population and varying social and economic levels, looks like a statistical minimum, yet it is not. In Brooklyn, for instance, hemorrhage continues to be the principal cause of maternal death. The causes of death appear in Table I. The controllable factors set down in Table II need no elaboration.

TABLE I. MATERNAL DEATHS, BROOKLYN, 1950

Abortion	7
Ectopic	2
Infection	5
Toxemia	12*
Anesthesia	3*
Hemorrhage	12*
Total	41
Official total	38 (provisional)

*One case officially nonpuerperal.

TABLE II. CONTROLLABLE FACTORS, 1950

Anesthesia		3	
Abortion (all induced)		6	
Infection		5	
Toxemia		12	
Hemorrhage and shock		15	
Cesarean Section.—		*Hemorrhage.*—	
Anesthesia	1	Abortion	1
Hemorrhage	5	Ectopic	2
Infection	1	Cesarean section	5
Toxemia	1	Rupture of uterus	3
		Other	4

It has always been true that diligent search through the nonpuerperal causes of death associated with pregnancy will reveal cases with clear-cut controllable factors. It seems clear that puerperal deaths assigned to nonpuerperal causes will increase in number under the new classification. We are not interested in the statistics, but in the deaths. In our search for the controllable factors of maternal death we cannot depend upon the statistician alone, but must continue to examine not only the certificate of death but actual

case reports. The risk of cardiac disease can be evaluated in no other way, and deaths directly due to anesthesia will either not be found or will be tabulated separately as "therapeutic misadventure in anesthesia" (E 954).

Hemorrhage will continue to remain the principal cause of maternal death just as long as blood remains hard to get. In spite of the old statistics to the contrary, it, in all probability, was never any different. The mechanical form of good prenatal care will not reduce the death rate from toxemia until it is widely accepted that prenatal care requires as much experience as the conduct of delivery itself. Puerperal infection has not disappeared. It responds to our new therapy, but not always. The majority of cases are associated with prolonged labor and hemorrhage; and the organisms present before labor are not important in its causation.

As the death rate shrinks, interest will lag and consciousness of our responsibility may wane. Perhaps we have underestimated the size and scope of the problem, in that we have paid scant attention to infant mortality rates. The trend of infant mortality has been steadily downward, with the 1948 rate the lowest ever recorded.[2] The mortality is much higher in the first day of life than in any succeeding age group. The mortality of infants under 1 day of age was a third of the total infant mortality in 1948.[2] Little ground has been gained in the reduction of infant mortality associated with the complications of pregnancy. As might be expected, nearly all deaths from premature birth, and injury at birth, and two-thirds of the deaths from congenital malformations take place during the first month of life.

Just as the obstetrician is interested in fetal salvage, the pediatrician is concerned with prenatal and delivery care. The mechanism for maintenance of joint interest, however, is not the great obstetric conference which has been so effective in reduction of the maternal death rate. The very number of infant deaths, and the difficulty of obtaining positive death data make that impractical. It is not necessary and it may not be wise to add still another staff conference to the heavily weighted hospital program. In each hospital, however, the Department of Obstetrics and the Department of Pediatrics, as a joint project assigned to a responsible individual of each staff, should keep a running record of their infant mortality. Stillbirths and neonatal deaths, for example, may readily be set up in percentage columns; and month after month in cumulative statistics and year after year experience will be known. In some areas a central agency may make comparisons or teaching conferences may be conducted. No longer may it be said, as it can now, that many obstetricians do not know what their infant mortality really is. For obstetricians and pediatricians the maternal mortality remainder lies just ahead.

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Department of Case Reports
New Instruments, Etc.

CONTINUOUS OBSERVATION OF THE FETAL HEART

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IT IS often desirable, clinically and experimentally, to observe the fetal heart continuously for long periods of time. It is possible to do this with an ordinary stethoscope, but variations in rate other than grossly rapid ones cannot be accurately observed in this way; and the method is very arduous if a long period of time elapses. The advantages of a written, continuous record are obvious in experimental work. It therefore seemed of value to construct a device which would produce this written record, and in addition would allow auscultation to be carried out easily and without fatigue. This device is now in use in the Labor Rooms of the Sloane Hospital for Women.

Such a device consists of three chief parts: (1) a "pick-up" or receptor, (2) an amplifier, and (3) either a recorder or a loud-speaker.

The "pick-up" is an instrument which "picks up" the sound of the fetal heart through the mother's abdominal and uterine walls. The maternal tissues conduct sound poorly because of their softness and thickness. It is necessary to make pressure *into* the abdominal wall (as is done with the bell-type stethoscope) in order to obtain the loudest sounds. The instrument found most satisfactory for this purpose is the "Heartbeat Pick-up."* This is a displacement type crystal instrument which has a projecting cylinder covered by a rubber diaphragm about 3 cm. in diameter. This cylinder allows effective pressure to be made into the abdominal wall. The instrument has a flat frequency response from 1 to 600 cycles per second, and will record frequencies as high as 7,000 cycles per second.

The output from the "pick-up" is fed either into the system for continuous written recording or into the system for loud-speaker reproduction. When a written record is desired, the output is fed into the amplifier developed in accordance with the plan, as shown in Fig. 1. The amplifier then drives a direct ink-writing recorder. If, during observation, it is desired to listen to the fetal heart, a pair of earphones designed like a stethoscope† may be switched in.

The amplifier is designed to cut off rapidly below 35 cycles per second, and the resulting over-all response of the system is shown in Fig. 2. This lower limit of frequency response is chosen because it yields a clear trace highly suitable for recording rate (Figs. 3 and 4, lower tracings). When the frequency response is extended flat to 20 cps, the type of record shown in Figs. 3 and 4, upper tracings, is obtained. This record is more complicated, though more inclusive, and is much more difficult to interpret. It has been felt unnecessary to incorporate high-frequency compensation in order to extend the upper range of the recorder.

In actual operation, the "recorder" can be run at three different speeds: 0.5, 2.5, and 12.5 cm. per second. Fig. 3 is a record obtained at 0.5 cm. per second. It shows a clear record from which rate is readily calculated, and the recorder can be run for long periods

*Manufactured by the Brush Development Company, Cleveland, Ohio, Model DP-IH.
†"Monoset" Model 4625, Telex, Minneapolis, Minn.

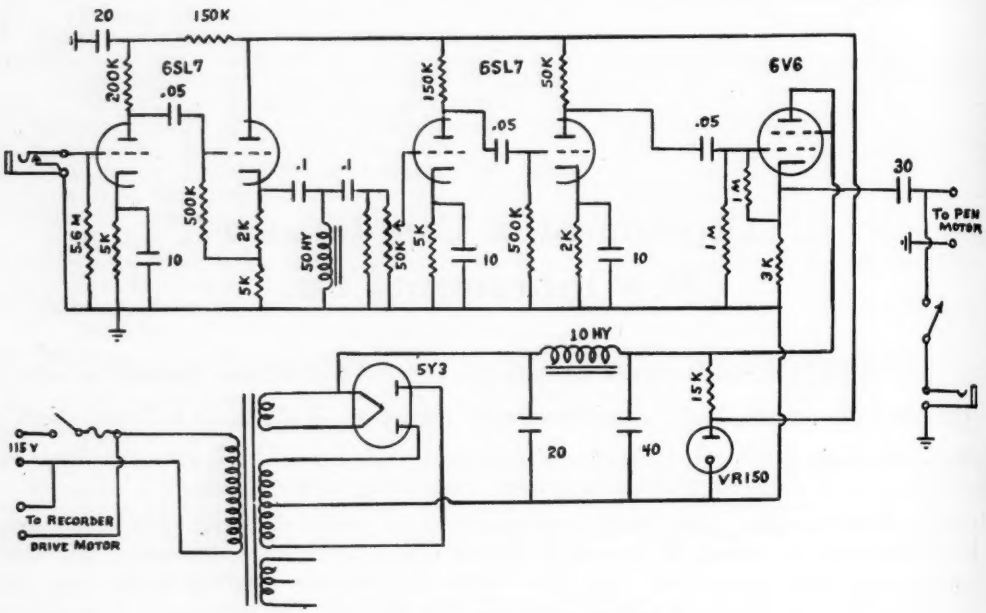

Fig. 1.—Amplifier for direct recording.

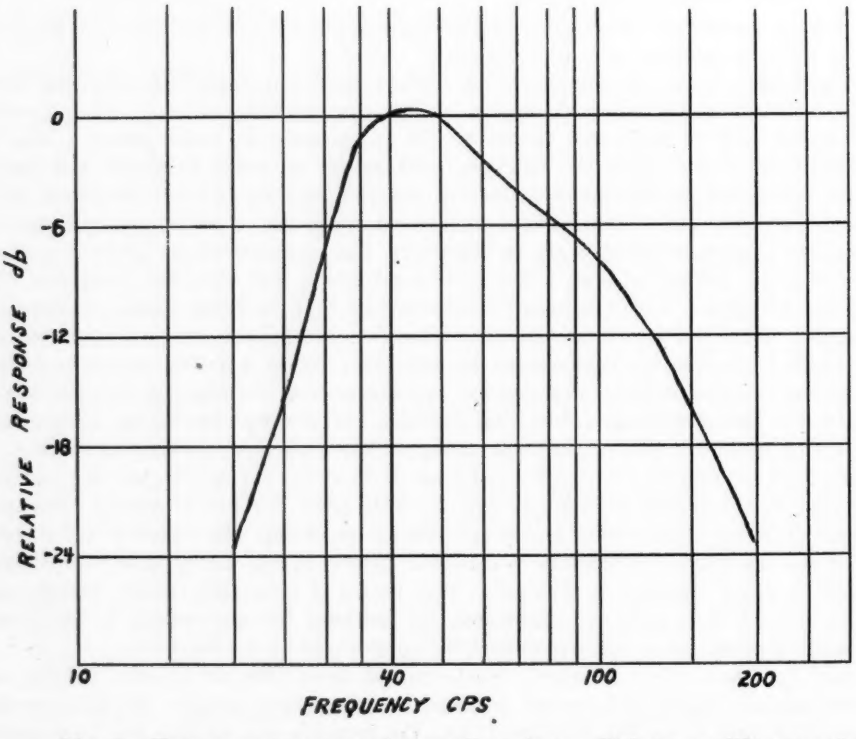

Fig. 2.—Frequency response of over-all system: Pick-up-amplifier-recorder.

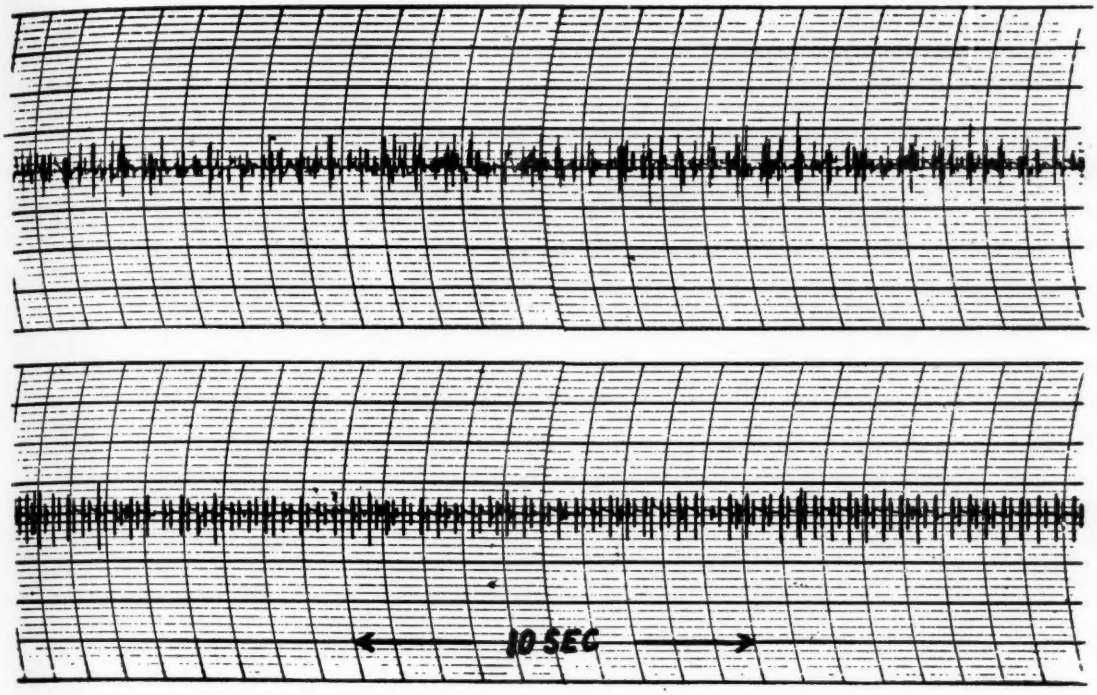

Fig. 3.—Slow speed recording of fetal heart from abdominal wall. Chart speed 0.5 cm. per second. Direction left to right. Upper tracing: frequency response flat to 20 cycles per second. Lower tracing: frequency response cut off at 35 cycles per second.

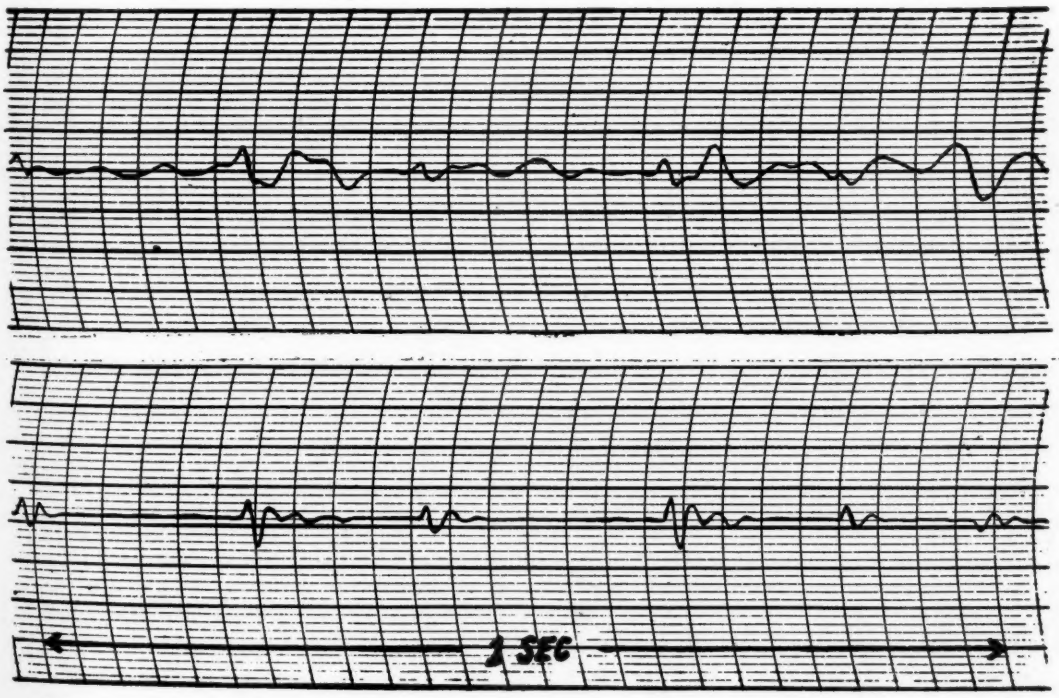

Fig. 4.—Same as Fig. 3, but chart speed 12.5 cm. per second.

at this speed without paper wastage. Fig. 4 is a record from the same patient, with a recorder speed of 12.5 cm. per second. This speed is useful when it is desired to study the individual waves in greater detail.

When it is desired to listen to the fetal heart for long periods over a loud-speaker, the output of the pick-up is fed into a standard audio-amplifier* which drives an eight-inch dynamic loud-speaker. This system possesses adequate amplification, but acoustical feed-back presents a serious problem. In order to reduce this feed-back it was found necessary to modify the amplifier in such a way that the gain falls off relatively rapidly above 60 cycles per second. In addition, the output impedance (No. 2 input of the Bell amplifier) has been increased by removing the 22 thousand ohm resistor. With these modifications, the system in most instances will produce a sound entirely adequate for study or for demonstration.

*Bell Sound Systems, Inc., Model 2122.

LEUCEMIA AND PREGNANCY*

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THE association of leucemia with pregnancy is infrequent. Only 108[6] such cases have been recorded in the literature to date, and of these, only two were of the acute monocytic type. In the past ten years at Jefferson Medical College Hospital, among 23,748 deliveries, there has not been a single case of monocytic leucemia.

The rarity of pregnancy complicated by leucemia is thought to be due to the massive leucemic infiltration of the genital tract which produces a secondary amenorrhea.[1] This filtration is sometimes so abundant that the ovarian tissue may be completely destroyed.[3, 5] The occurrence of amenorrhea is so common in the presence of chronic leucemia that conception may take place with the diagnosis not made or in doubt.

The monocytic form of leucemia occurs in 2 to 20 per cent of all types of leucemia.[4] As mentioned above, we have been able to find in the literature only two previous cases of acute monocytic leucemia complicating pregnancy. The general considerations of leucemia complicating pregnancy are applicable as well to the monocytic type herein reported.

The first known case of monocytic leucemia complicating pregnancy was reported in 1948 by Williams,[8] in which the illness ostensibly began at the seventh month. The patient was delivered by cesarean section, under continuous spinal anesthesia, of a normal, living, 5 pound, 12 ounce male infant. Death of the mother occurred twelve days after operation.

A more recent case was reported in 1949 by Birge and associates.[2] Illness also occurred in the seventh month, complicated by eclampsia, and the patient delivered prematurely a nonviable infant. The infant did not show any evidence of congenital leucemia. The mother had a remission, only to have an exacerbation twenty-one months later with prompt death.

The case herein presented is one of acute monocytic leucemia associated with pregnancy.

The patient, T. T., a 24-year-old Negro woman, gravida i, para 0, was admitted to Jefferson Medical College Hospital as an acute emergency case on Jan. 18, 1950. Her last normal menstrual period was May 31, 1949, and her expected date of confinement was March 10, 1950.

Her pregnancy had been uneventful, but without prenatal care, until Dec. 6, 1949, when she noticed a swelling and soreness of the right side of the neck and attended the Prenatal Clinic at Harlem Hospital in New York City. There were six subsequent visits to this institution plus one visit to another hospital, and she was advised to have a biopsy of this progressively increasing mass in the neck. The provisional diagnosis was mumps, mastoiditis, or some blood dyscrasia. Because of enlargement of the mass with involvement of both sides of the neck, difficulty in swallowing solid foods, and intense dyspnea, the patient was referred to Dr. Tocantins of the Hematology Department of the Jefferson Hospital, who immediately admitted her to the Maternity Ward.

Her past medical history revealed the usual childhood illnesses. There was no history of other significant illnesses, operations, or treatment with sulfonamides or specific drugs. The significant physical findings on admission were:

(1) Temperature 98.6° F.; pulse 90; respirations 30; blood pressure 114/74. (2) Dyspnea and orthopnea. (3) Pale mucous membranes. (4) Hypertrophy of the gums. (5) Swelling of the entire neck with large, discrete, firm, nontender nodes, palpable es-

*Read before the Philadelphia Obstetrical Society, Jan. 4, 1951.

pecially in submandibular areas. (6) Generalized lymphadenopathy. (7) Minimal basal râles of both lung fields. (8) Two plus pretibial edema. (9) Petechial hemorrhages over osseous prominences. (10) Normal neurologic reflexes. (11) Hypertrophied breasts.

The abdomen was enlarged to the size of a 28 to 30 weeks' gestation with the fundus four fingerbreadths above the umbilicus. The vertex was floating and the fetal heart sounds were heard in the right lower quadrant, with a rate of 140. The spleen and liver were not palpable because of the enlarged uterus.

On admission, the laboratory findings were: hemoglobin 57 per cent, 8.84 Gm.; red blood cells, 2,710,000; white blood cells, 65,000 with 87 per cent monocytes; platelet count, 88,000; normal bleeding time, coagulation time, and prothrombin time. The presence of petechiae with a normal bleeding and coagulation was considered most unusual. The Fishberg concentration test was 1.020, the urea clearance 100 per cent; serum bilirubin, 0.2 mg.; plasma proteins, 6.47 Gm.; urea, 3.6 mg.; and uric acid, 6.6 mg. The eye grounds were normal.

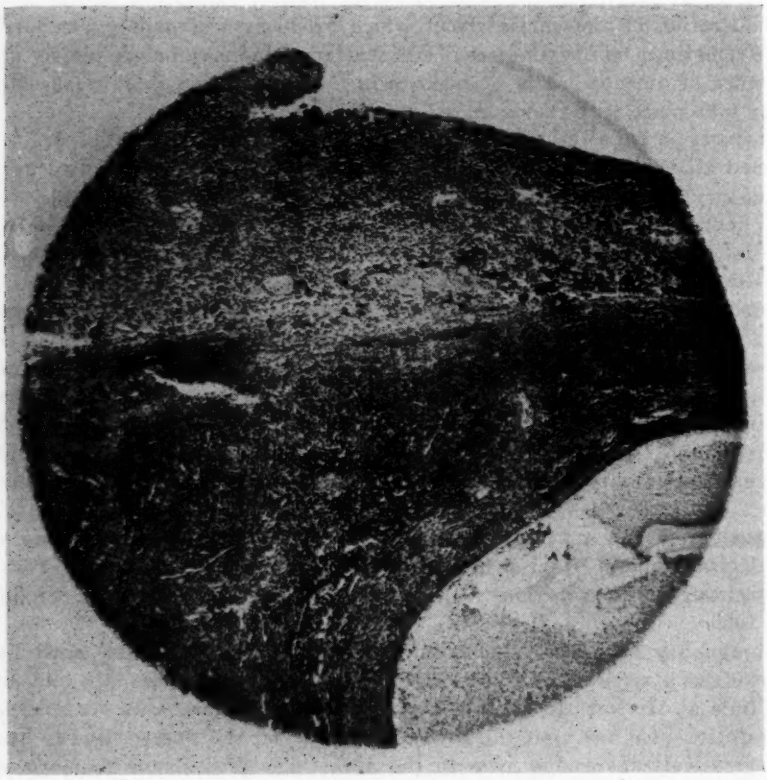

Fig. 1.—Ovary. Note diffuse monocytic infiltration. (×50.)

X-ray of the abdomen revealed the fetus to be probably of about 7 months' gestation. X-ray of the neck and chest confirmed the physical findings.

Bone marrow aspirations and smears confirmed the diagnosis of acute monocytic leucemia. Because of threatened respiratory embarrassment with a distinct possibility of death, an emergency cesarean section was decided upon.

Preoperatively the patient received one small x-ray treatment to the neck and suprasternal area in an effort to reduce the mediastinal constriction and relieve the dyspnea.

On January 20, two days after admission, under local anesthesia (1 per cent procaine) and a minimal amount of intravenous Pentothal Sodium, a classical cesarean section

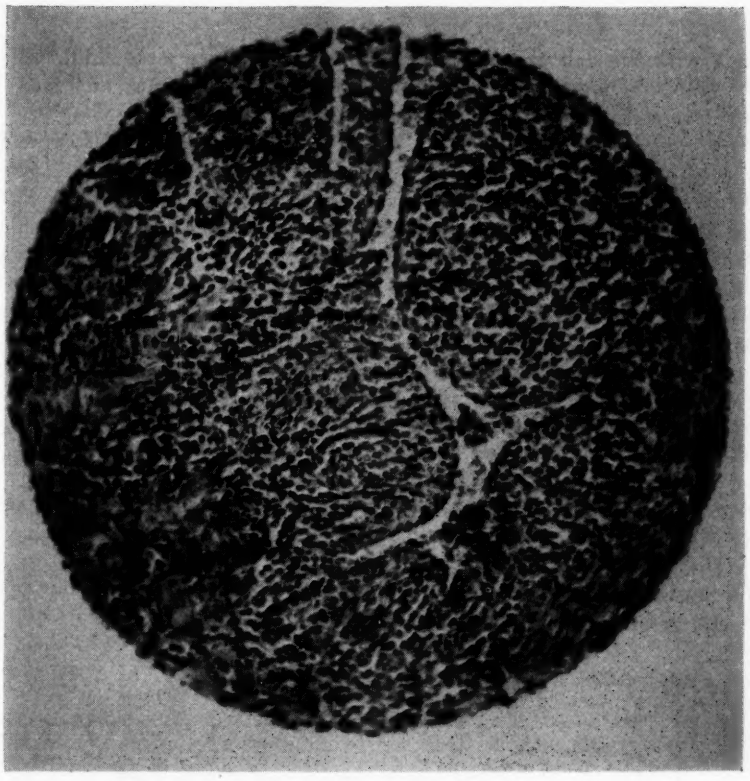

Fig. 2.—Uterus. Note dense infiltration of leucemic cells. (×200.)

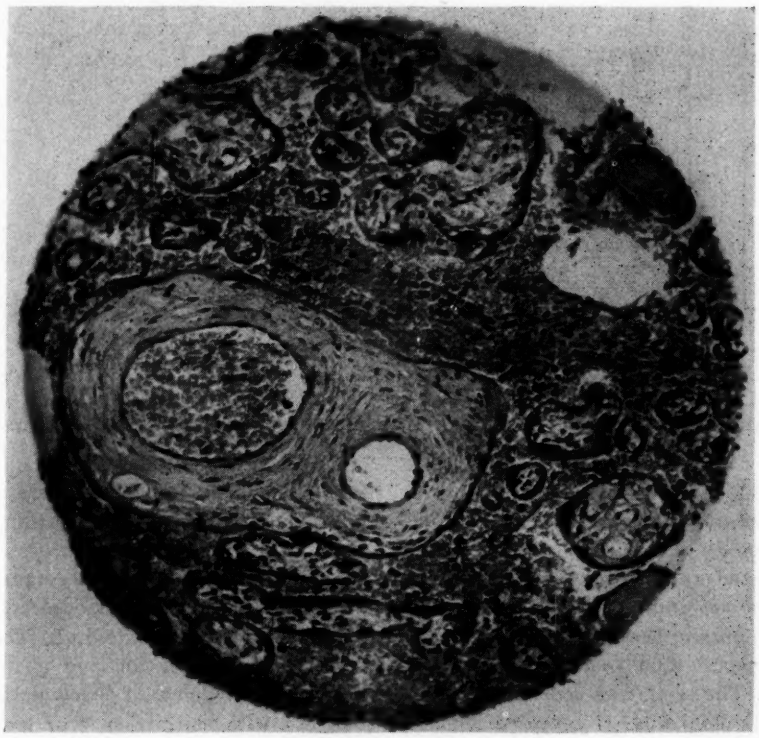

Fig. 3.—Placenta. Note leucemic cells in intervillous spaces but only normal blood cells in chorionic villi. (×200.)

was performed with the delivery of a viable 5 pound, 3 ounce male child. Bleeding from the operative site was more than usual, especially from the skin, and was finally controlled by suturing strips of Hemopak to the wound.

Postoperatively, the patient was put in an oxygen tent and her treatment consisted of nitrogen mustard, 9 mg. in divided doses; blood transfusions, 8 units (500 c.c. each); penicillin, over 4 million units; streptomycin, 0.5 Gm. twice a day for a total of 16 Gm.

The significant blood studies postoperatively were a sickling trait, a blood platelet decrease from 88,000 to 28,000, a gradual decrease of leucocytes from 65,000 on admission, so that at the time of death the count was 3,600 with 88 per cent monocytes.

The clinical course after operation revealed remarkable improvement at first with nitrogen mustard. The patient was out of bed on the third postoperative day. The swelling, dyspnea, edema, and vomiting disappeared, only to reappear on January 27, her eighth postoperative day. Her temperature became elevated and never returned to normal, averaging about 100° F. The wound did not heal properly—moderate gaping of the incision persisted. There was minimal abdominal distension a few days after operation, but this became progressively worse and ascites was recognized on January 28, nine days postoperatively. X-ray confirmed this physical finding, and 3,000 c.c. of fluid were obtained by paracentesis. The abdomen gradually refilled with fluid. The patient was transferred to Women's Medical Ward on February 2, and her course was gradually downhill with increasing respiratory embarrassment due to pleural effusion. She died on Feb. 12, 1950, twenty-three days after operation.

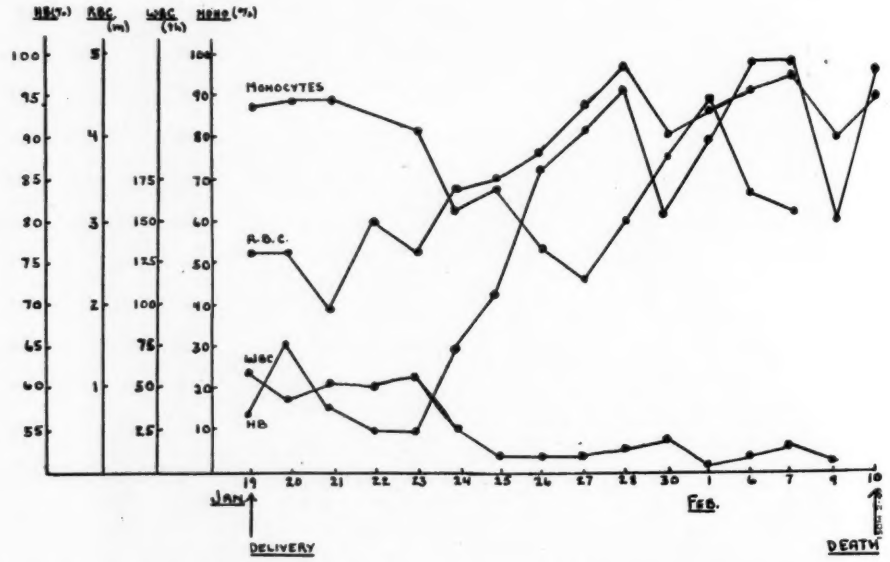

Fig. 4.—Chart of patient illustrating the rise in hemoglobin and red blood cells and monocyte count with progressive drop in white blood cells.

The baby showed no physical abnormalities. Repeated blood counts were normal, the only significant finding being a sickling trait. Subsequent physical examination and hematological studies on the baby revealed a normal infant.

A limited autopsy was permitted on the abdominal organs. All the organs revealed dense monocytic infiltration. The placenta weighed 410 grams and measured 23 cm. in diameter. Grossly, the fetal surface was smooth, pale gray, and glistening. The maternal surface was pink and ischemic, with numerous areas of calcification and no evidence of infarction. The cord was eccentrically inserted with no evidence of leucemic cells in the vessels. Histologically, it revealed a mature placenta with the presence of leucemic cells in the intervillous spaces but normal blood cells in the chorionic villi.

Pathologist's Report.—

Ovary: Both ovaries show irregular focal areas of thickening with fibrosis and diffuse monocytic cellular infiltration overlying the cortex. In addition, there is a monocytic infiltration of the meso-ovarium and the medulla which is predominantly perivascular about the capillaries and venules.

There are areas of diffuse hemorrhage alternating with these areas of monocytic infiltration on surface of the cortex.

Adrenal Gland: Although there is diffuse infiltration of both cortex and medulla, it is notable that the infiltration is more marked on the medullary portion and sparser in the cortex.

This suggests that the compactness with consequent increased tissue tension of the stroma in the cortex resists extensive infiltration.

Uterus: The endometrium contains very few glands in the stratum basalis. The stroma shows marked vascularity with dilatation and hyperemia of the capillaries, and dense and diffuse infiltration of monocytic cells. In local areas, the endometrium is completely lacking and hemorrhage on the surface is a pronounced feature.

The myometrium shows extreme and diffuse venular and capillary dilatation and congestion, with marked endothelial proliferation. There is a dense diffuse infiltration of leucemic cells which is most pronounced in perivascular areas from which it extends into the interstices with consequent slight to moderate atrophy of the muscle fibers.

The infiltration extends with intensity through all portions of the myometrium and into the parametrium.

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ENDOMETRIOSIS OF THE OMENTUM SUGGESTING ORIGIN IN CELOMIC MESODERM*

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THE question of etiology of endometriosis has long been in doubt. Three major theories have been proposed. Sampson[1] in 1921, in his classical description, advanced the "implantation" theory. Other opinions have opposed Sampson's theory in postulating origin from abnormal differentiation of celomic mesoderm. Evidence in favor of the "implantation" theory is the demonstration of regurgitation of sloughed endometrium through the uterine tubes during menstruation. The distribution of endometiosis is said to correspond with the route of material passed from the fimbriated tubal end. The uterine tubes are usually patent in patients with endometriosis. Also, implants of endometrium grow in the peritoneal cavity of experimental animals. However, critics of Sampson's theory suggest that although endometrial fragments may be passed through the human uterine tubes into the peritoneal cavity, they are so profoundly degenerated, if not actually dead, that they would not grow after deposition. Furthermore, endometrial lesions not on the serosal surface of the pelvis can hardly be explained by the "implantation" theory. Transplantation by lymphatic or blood vessels is possible since endometrium has been seen in lymphatics and in lymph nodes.[2] However, endometriosis arising in this way seems improbable since the location of endometriosis does not correspond with the lymphatic flow from the uterus.

The concept of abnormal differentiation of celomic mesoderm, as promulgated by Meyer,[3] explains the lesions located within the uterus, on the pelvic serosal surfaces, and in deeper structures of the celomic cavity including the extremities. Since the anlage of the uterus and tubes is formed from an invagination of the primitive celom, it follows that the same differentiation is possible from other parts of the celomic mesoderm. In unusual cases of endometriosis, in the extremities, for example, endometriosis appears to arise from prosoplasia of mesenchyme of the celomic wall which is carried into the limb buds during formation of these organs.[4] If endometriosis is to be strictly accounted for by assuming differentiation from celomic mesoderm, there should be close relationship to the fully differentiated mature structure, the uterus. In the recent case herein presented, this relationship was suggested.

Case Report

The patient was a Negro woman, 33 years old, who had had four children. She complained of low back pain which occasionally radiated into the left groin. This pain had become progressively worse, especially in the last two and one half years. The pain was aggravated during her last pregnancy which had terminated one year before, and was more severe during menstruation. On Feb. 2, 1949, after roentgenograms demonstrated a spondylolisthesis of the fifth lumbar vertebra on the sacrum, an arthrodesis of L-4 to S-1 was done, and a body cast applied. On Oct. 24, 1949, she was readmitted with complaints of pain in the left side of the abdomen and fatigue. The patient described the pain as the same that had existed before, not having been relieved by the arthrodesis. The past history disclosed an appendectomy in 1925 and a laparotomy with uterine suspension in 1939. The operative diagnoses of pelvic endometriosis and ovarian cyst were made at the latter operation.

*The opinions and views set forth are those of the author and are not to be considered as reflecting the policies of the Navy Department.

Physical examination was not pertinent except for the pelvic examination. A purulent vaginal discharge was present and there was a small cervical erosion. The uterus was felt to be slightly enlarged, anteflexed, and deviated to the left. A firm, nodular mass about the size of a normal uterus was attached on the right uterine border.

Fig. 1.

Fig. 2.

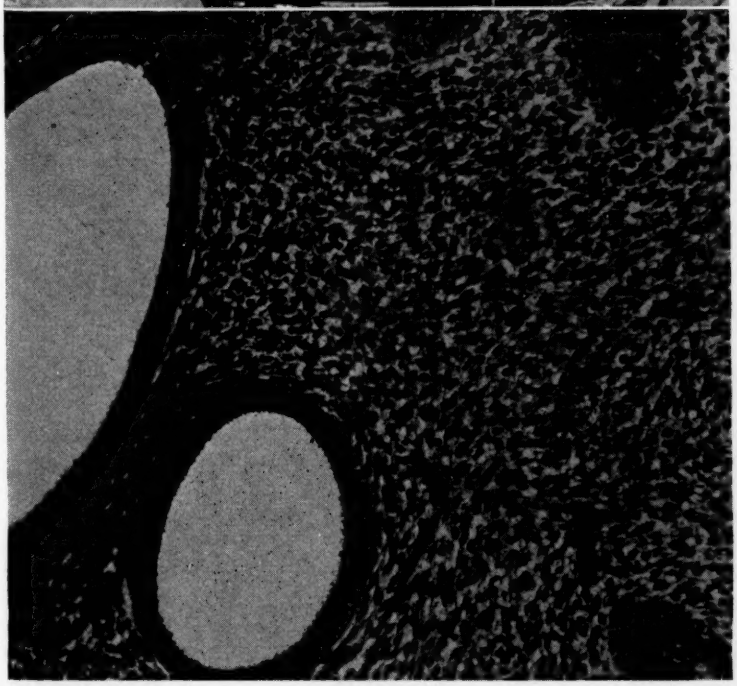

Fig. 1.—A portion of the omental cyst wall. (×35.)
Fig. 2.—Endometrial glands and stroma. (×200.)

A total hysterectomy and bilateral salpingo-oophorectomy were done. The omentum contained a nodule about 1 cm. in diameter, which had no connection with the uterus, uterine tubes, intestines, or other abdominal structures. Endometrial "implants" were seen throughout the pelvis and on the serosal surfaces of the uterus, tubes, and ovaries.

Fig. 3.

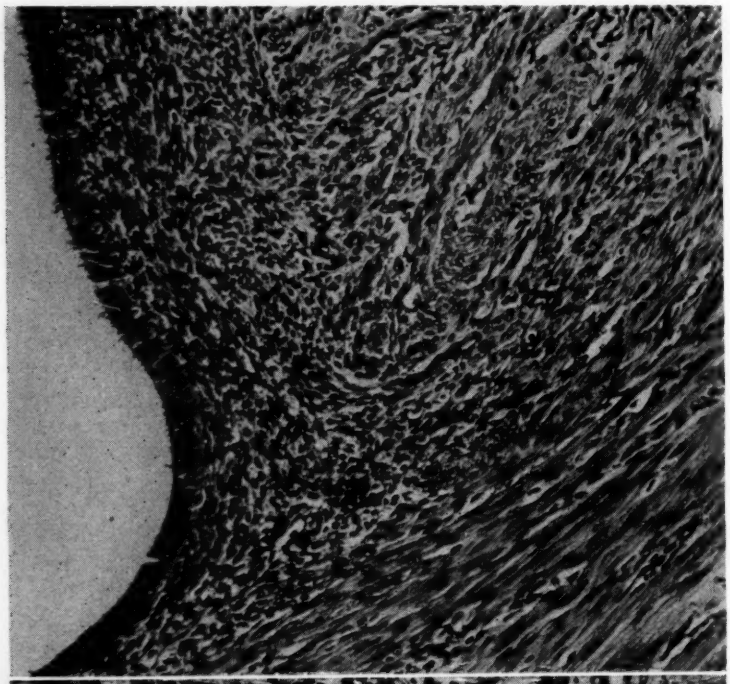

Fig. 4.

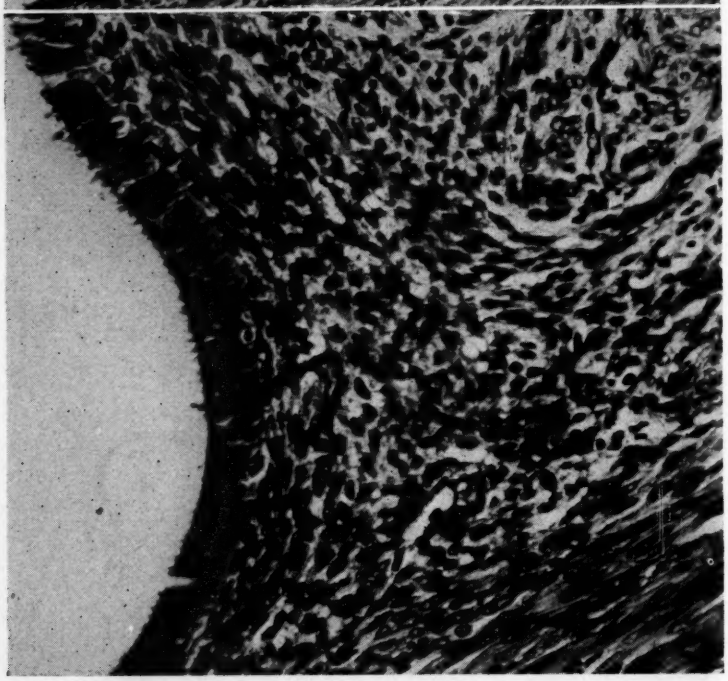

Fig. 3.—The photograph shows smooth muscle next to an endometrial gland and stroma. (×200.)

Fig. 4.—Detail of Fig. 3 to show smooth muscle and endometrial stroma. (×400.)

Pathological Examination.—The gross pathological specimen consisted of uterus with cervix, tubes, ovaries, and a piece of omentum which measured 2 cm. in diameter. Three pale blue nodules were present on the uterine serosa. The largest nodule was at the junction of the right uterine tube with the uterus and measured 1 cm. in diameter. The ovaries were cystic. When the blue nodules on the serosal surface were opened, a dark brown viscid material escaped. The ovarian cysts contained a watery brown fluid. Section through omentum revealed a fibrous, thick-walled, multilocular cyst, measuring 1 by 0.8 by 0.2 cm. It contained a brown, gelatinous material.

Microscopic examination of the blue serosal nodules revealed endometrial glands and stroma. Sections through the ovaries revealed corpus albicans cysts. Sections through the nodule in the omentum resembled a miniature uterine cavity lined with endometrial glands and stroma, and surrounded by smooth muscle suggesting myometrium (Figs. 1 to 4). The smooth muscle showed typical morphology on hematoxylin and eosin staining, but special stains were also used to differentiate it from the peripheral fibrous tissue. These stains included Mallory's aniline blue, Masson's trichrome, Van Gieson's picro-acid fuchsin, and Mallory's phosphotungstic acid hematoxylin. All of these were used with control sections made from the largest serosal endometrium of the uterus. With all methods used the smooth muscle of the omental endometrioma stained exactly as did that of the uterus.

Comment

The finding of all elements of the uterine cavity, including the myometrium, in an endometrial cyst of the omentum, gives strong evidence that the origin of endometriosis is abnormal differentiation of celomic mesoderm, since endometrial "implants" would not include muscle.

Endometrial lesions in the uterus, ovary, or certain other tissues which contain smooth muscle seem to stimulate proliferation of the inherent smooth muscle at the periphery. However, the presence of smooth muscle around an endometrial lesion in the omentum indicates that it is possible that all of the elements of an endometrioma can be derived from celomic mesoderm since smooth muscle is not a normal tissue of the omentum.

The smooth muscle was considerably greater in amount than would be inadvertently transferred by a forceps or other instrument, and it had a regular arrangement around the endometrial cyst. Still, there is a possibility that the smooth muscle arose from a bit of uterine wall or other smooth muscle transplanted into the omentum at the previous pelvic operation.

Also, it is possible, but unlikely, that a pedunculated serosal endometrioma was detached from the uterus and engulfed by the omentum.

The presence of endometriosis in the omentum, not attached to intestine or other structures, is most unusual. In a review of the literature, only one previously reported case was found.[5] This was much like my case, having smooth muscle around endometrial glands and stroma and being not attached to other structures. It was considerably larger, however, being "double-fist" in size.

The omentum is formed from splanchnic mesoderm which is associated with the entoderm.[6] This mesoderm has the same origin as the remaining part of the celomic mesoderm. It would be expected, therefore, that the mesoderm of the primitive mesentery possessed latent possibilities of abnormal differentiation to form structures found elsewhere in the celomic mesoderm, e.g., uterus. It is postulated that this prosoplasia arises from a mesodermal rest which responds excessively to the hormonal environment of the adult female, from adult omentum due to abnormal exciting influences, or from an unusually rapid or prolonged development of the mesoderm. Whatever the exact etiology, the lesions of endometriosis as found in this case would appear to represent an anomaly of development due to abnormal differentiation of the celomic wall. Whether there is secondary spread of endometriosis from these primary lesions by actual implantation is still in question. This appears possible, especially as the frequent rupture of endometrial cysts allows their contents to spill over the peritoneal surface. However, it is still doubtful that this sloughed endometrium is viable.

Summary

A case of endometriosis of the omentum containing smooth muscle is presented. This case suggests that some, if not all, lesions of endometriosis represent abnormal differentiation of celomic mesoderm, rather than "transplantation" of endometrium through the Fallopian tubes.

There was associated pelvic endometriosis.

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INFECTIOUS HEPATITIS DURING PREGNANCY AND ITS EFFECT UPON THE FETUS

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THE purpose of this report is to present an unusual case in which the patient, a multigravida, was affected with infectious hepatitis approximately one month before conception and was jaundiced during the entire course of her pregnancy. The pregnancy was terminated at the end of the thirty-second week of gestation and the fetus was a composite monster.

The patient, a 27-year-old multigravida, was first seen on June 18, 1949, at which time she complained of headache, right upper quadrant pain, loss of appetite, langour, malaise, apathy, and jaundice of three days' duration.

A review of the past history was significant in that the patient had several bouts of jaundice during her life. When she was twelve years old she had a long siege of jaundice and was confined to her bed for about a month. During her second pregnancy the patient became jaundiced at about the eighth month of gestation and she remained jaundiced until after the baby was delivered.

In August of 1947, following an incomplete abortion, it was necessary to perform a dilatation and curettage and to give this patient 1,000 c.c. of whole blood by transfusion.

The patient has had four miscarriages at from two to four months of gestation.

Family and social histories were essentially negative.

Physical examination revealed a temperature of 99.8° F., pulse of 62, and blood pressure of 120/72. The patient was a well-developed, well-nourished white woman of the stated age who appeared acutely ill. The skin was warm and dry and had a distinct yellow cast. The scleras of the eyes were also yellow and the pupils reacted equally to both light and accommodation.

Except for tenderness over the liver area in the right upper quadrant of the abdomen, the rest of the body physically was essentially normal.

Laboratory work done at this time revealed a red blood count of 4,720,000; hemoglobin 15 Gm. (95 per cent); white blood count 6,200 with an essentially normal differential count. The icterus index was 60 units; prothrombin time 100 per cent; cephalin flocculation 2 plus; and urine urobilinogen was negative. A Van den Bergh reaction gave a 6.9 mg. per cent direct reaction and a 9.1 mg. per cent indirect reaction.

At this time, a presumptive diagnosis of infectious hepatitis was made and the patient was sent home to be confined to absolute bed rest. She was placed on a high carbohydrate, high protein, low fat diet, in addition to which she was started on Methionine 1.0 Gm. three times a day and one multiple vitamin capsule three times a day.

The patient was followed closely at home. In a few days, the liver became palpable below the right costal margin. However, her condition seemed to progress favorably until Aug. 17, 1949, when she reported that her last menstrual period was June 22, 1949. A pelvic examination at that time revealed a positive Hegar's sign and the uterus was enlarged to a size consistent with a six weeks' pregnancy.

On August 24 the patient was hospitalized for the express purpose of having a therapeutic abortion performed, but after several consultations it was decided to allow her to continue with the pregnancy but to follow her closely with frequent visits and laboratory studies as checks on her liver function.

Additional laboratory studies at this admission revealed little change in the original studies except for a decrease in hemoglobin to 11.5 Gm. (73 per cent) and a decrease of the red blood count to 3,940,000. X-ray studies of the gall bladder revealed a nonfunctioning organ without evidence of stones. A flat plate of the abdomen failed to reveal abnormalities.

On the fourth hospital day, the patient was discharged to continue the preadmission regime with the addition of choline chloride, 0.5 Gm. at meal times, and ferrous sulfate, 5 grains after meals.

Clinically, the patient improved as the pregnancy progressed until toward the end of the sixth month of gestation, at which time she developed a streptococcus pharyngitis with a temperature of 104° F. This infection responded slowly to penicillin therapy and, after this cleared, clinical signs of advancing liver failure were noted. There was an increase of jaundice, anorexia, and malaise. The liver increased in size and could be palpated three fingerbreadths below the right costal margin and there was three plus ankle edema. The total proteins had decreased to 5.20 Gm./100 c.c. and the albumin fraction decreased to 3/65 Gm./100 c.c.

At this time her case was presented to the combined obstetrical and gynecological staff of Toledo Hospital at their regular meeting. It was their opinion that if by additional protein therapy by mouth and by vein, if necessary, the patient could be carried through to the eighth month of gestation, medical induction should be done at that time and a viable baby could then be expected.

She was placed on a protein hydrolysate, 100 mg. twice a day, in addition to her already high protein diet, and in one month the total protein had risen to 5.85 Gm. and the albumin fraction had risen to 3.70 Gm. During the two weeks prior to admission she was also given 2 mg. of vitamin K three times a day.

On March 1, 1950, the patient was admitted to the Toledo Hospital for an attempt at medical induction of labor. Laboratory work on this admission revealed a red blood count of 4,470,000; hemoglobin 14.0 Gm. (89 per cent); white blood count 11,000 with a normal differential; the direct Van den Bergh was 5.6 mg. per cent and the indirect reaction was 6.9 mg. per cent; the icterus index was 70 units; the prothrombin time was 100 per cent; the cephalin flocculation was three plus; thymol turbidity was 13.2 units; the serum proteins were 5.85 Gm. per 100 c.c. with the albumin fraction 3.70 Gm.; a red blood cell fragility test showed beginning lysis at 44 and complete lysis at 32; the hematocrit was 42 per cent; and the alkaline phosphatase was 2.2.

The patient was then given 5 minims of Pitocin in 500 c.c. of 5 per cent glucose in water at the rate of 14 drops a minute. After an uneventful labor she was delivered of a composite monster.

The composite monster had six digits on all four extremities. It also had bilateral hare lip and cleft palate. There was a huge omphalocele, also a spina bifida with a large meningocele. There was a deformity of the ears and because of maldevelopment it was impossible to determine the sex of the infant. At postmortem examination, there was found a patent intraventricular septum in the heart and a calcific ring was noted in the aorta just proximal to the arch.

The patient made an uneventful recovery and went home on the seventh postpartum day. She returned one month later to Toledo Hospital to undergo an exploratory laparotomy.

A transverse incision in the right upper quadrant of the abdomen was used and the liver and gall bladder were exposed. The liver was a dark green, nearly black color. It was normal in size and a little firmer than usual in consistency. There were no nodules. The gall bladder was slightly distended and was filled with many small stones. A cholecystectomy was then performed and the common duct was exposed and isolated. The common duct was quite small but there was no evidence of inflammation old or new. The common duct was then opened and a probe was passed easily into the right and left

hepatic ducts as well as into the duodenum. No obstruction was met. A No. 11 T tube was placed in the common duct with difficulty. Subsequent cholangiograms were reported as normal by the x-ray department.

A wedge-shaped biopsy was taken from the anterior surface of the liver and there appeared to be less bleeding than normal during the procedure.

The wound in the upper abdomen was then closed and a small incision was made in the midline above the symphysis and a bilateral tubal ligation performed. This wound was then closed and the patient was returned to her room in good condition.

She left the hospital on the fourteenth postoperative day and since that time she has been getting steadily better. The jaundice has decreased and, at the last check, the icterus index was 19. Plasma proteins have increased to 6.0 Gm. per 100 c.c. She is still on the same diet and is still taking essentially the same medication. She is seen once a week and her laboratory tests are checked every month.

The sections of the liver were submitted to the laboratory of Toledo Hospital where a diagnosis of slight pericholangitis was made. Dr. Howard T. Karsner also reviewed the slides and reported, "Her liver has completely recovered in so far as the morphology is concerned."[1]

At the time of the writing of this paper (Nov. 30, 1950) the blood studies reveal in addition to the icterus index of 19: cephalin flocculation one plus; alkaline phosphatase 2.5 Bodanski units; thymol turbidity 6.6 units; prothrombin time 80 per cent; and a normal red and white blood count.

Comment

Infectious hepatitis, a virus disease that occurs in epidemic and sporadic forms, infrequently attacks pregnant women. DeLee and Greenhill[2] have reported only ten cases in 72,000 deliveries at the Chicago Lying-in Hospital. Other authors[3, 4, 5, 6] have also reported several cases that occurred during epidemics.

In each of the cases presented above the disease was contracted by the patient during the second or third trimester of pregnancy and in each case there was no fetal abnormality. In the case studied in this report, the disease was contracted approximately one month before conception and was present during the entire pregnancy. The question is therefore raised: Does the virus of infectious hepatitis pass through the placental barrier and enter the fetal bloodstream in sufficient quantity to cause the fetal abnormalities noted here?

Both clinical and experimental evidence exists that certain viruses can pass through the placental barrier from maternal to fetal circulation and infect the fetus in utero. One outstanding example is German measles. Zondek and Bromberg[7] concluded that the virus which causes infectious hepatitis was not able to infect the fetus in utero, either because it did not pass the chorionic barrier or because it circulated in insufficient amounts in the blood of the fetus to cause definite damage. It is again worth while to note that in none of their cases was the disease contracted during the first trimester and in order to injure the fetus the virus must be present in a high concentration during the period of formation. Of course, the case presented in this paper is an isolated case and further studies must be reported to substantiate the supposition that infectious hepatitis, when contracted during the first trimester, constitutes a severe threat to the fetus.

The question might then arise: Why was this patient not therapeutically aborted early? Nixon,[8] Zondek, and Bromberg,[9] in their articles, answer this question well.

Nixon[10] has stated that the pregnancy should be terminated only if the hepatitis was of such severity that the life of the expectant mother was in danger. Even then "it is controversial whether the evacuation of the uterus will influence final changes in the liver." One of the patients in his series died of acute yellow atrophy 48 hours after delivery of her child.

Zondek and Bromberg[11] have stated that, in their opinion, infectious hepatitis in the pregnant woman should be considered, above all, as an infectious disease complicating pregnancy. The general rules in the management of infectious diseases occurring during

pregnancy are applicable also to infectious hepatitis. The conclusion was reached that in severe cases artificial interruption of the pregnancy may aggravate the course of the disease and should be strongly discouraged. Therefore this patient was permitted to continue with her pregnancy and not until signs of impending liver damage were noted was the pregnancy interrupted.

Summary

1. A case was presented in which the patient was affected with infectious hepatitis approximately one month prior to conception. The hepatitis and/or jaundice persisted throughout the entire pregnancy.

2. The product of this conception was a monster.

3. The question is therefore raised, does infectious hepatitis, when contracted early in pregnancy by the mother, constitute a threat to the fetus? This question must await further reports for verification.

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TUBAL PREGNANCY COMPLICATING TUBERCULOUS SALPINGITIS

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EXTRAUTERINE pregnancy in the presence of tuberculous salpingitis is an extremely uncommon pathological condition, Wharton and Stevenson[1] stating that they believed it to be one of the rarest combinations seen in gynecology. These authors, reporting one case and surveying the literature up to 1939,[2] were able to find only 16 cases previously reported and in 8 of these the gestation sac was completely or partly free in the abdominal cavity. In the other 8 cases, the ectopic pregnancy was of a true tubal type. All of the previously reported cases had been in the foreign literature.

Bland,[3] in a more comprehensive study in 1940, was able to find 32 previously recorded cases and added a case of his own. A complete bibliography of these cases is included in this article. Rojel[4] in 1941 and Hicks[5] in 1942 each added single cases. Shannon and Heller[6] described a case in 1943 in which gestation had progressed to approximately five to six months. The patient died 24 hours after admission, autopsy revealing generalized caseous pelvic tuberculosis with multiple cold abscesses, generalized miliary tuberculosis of the lungs, liver, spleen, kidneys, and adrenals. The authors suggested that the prolonged development was due to previous tuberculous thickening of the tubal wall, preventing earlier rupture. Mann and Meranze[7] and Pink[8] each added cases in 1944. Subsequent single cases were reported by Villard[9] in 1945 and Pendl[10] in 1947. Haifetz[11] described a case in the foreign literature (not available to authors) in 1948. Thus a total of 41 cases have, to our knowledge, been previously reported.

In the 54 years the Pathologic Laboratory at the Free Hospital for Women has filed microscopic reports, there have been 197 cases of tuberculous salpingitis and 313 cases of tubal pregnancy. The case reported below is the first in this laboratory in which these 2 conditions have coexisted. Stevenson and Wharton[2] noted a similar correlation reporting 402 cases of tuberculous salpingitis and 516 cases of tubal pregnancy in a period of 47 years at the Johns Hopkins Hospital with one case of the conditions combined.

The following case is considered to be of interest because of its relative infrequence.

E. K. (Free Hosp. No. 38092), aged 22 years, was a white, para 0, housewife, married 2 years. She was first seen in the outpatient department of the Free Hospital for Women on July 20, 1948, complaining of a soft, flesh-colored growth just outside the left labium and an inability to become pregnant. The past history revealed only pleurisy of unknown etiology at the age of 14 years. The family history was negative and there was no known contact with tuberculosis. Menarche began at age 13 with regular periods every 28 days lasting 5 to 6 days. During the previous two years periods had occurred every 25 to 26 days. During alternate months she had noted nausea and vomiting and a bearing down sensation in the lower abdomen shortly after the onset of flow. The last menstrual period was on July 1, 1948, and the previous menstrual period June 6, 1948. Review of systems was negative except for a small amount of red blood noted in the stools for a 4-month period.

Physical Examination: The general examination was negative. Pelvic examination revealed a papilloma of the thigh near the left labium. The labia, introitus, vagina, and

cervix were normal. The uterus was forward, anteflexed and small. The vaginal vaults and adnexa seemed normal. A vaginal smear was reported as atypical benign and the patient was referred to the sterility clinic.

An endometrial biopsy taken in the sterility clinic on July 23, 1948 was reported as normal 22-day endometrium.

The patient was next observed in the outpatient clinic on May 16, 1950, because of vaginal bleeding and passage of tissue. The pathological report (S50-2132) on this material noted decidua suggestive of pregnancy but no chorionic villi, trophoblast, or placental site giant cells were seen.

She was next seen on July 19, 1950, complaining of irregular vaginal bleeding. The last apparently normal menstrual period had started on May 31, 1950. This was followed by daily staining throughout the month of June with severe cramps on June 29, associated with the passage of one large clot. Bleeding persisted until July 1, after which it diminished but daily staining still occurred.

Physical Examination: The patient was a well-developed, well-nourished woman in no distress. The general physical examination was negative. Pelvic examination revealed a normal introitus, vagina, and cervix. The uterine fundus was not well outlined because of abdominal tenderness but was thought to be somewhat enlarged. A tender, firm resistance was palpable on the right side but no definite mass was determined. There was a small amount of dark blood exuding from the cervix. A frog pregnancy test was negative. Urinalysis was negative.

On July 19, 1950, an exploratory laparotomy was performed, the preoperative diagnosis being ectopic pregnancy, right, probable tubal abortion. At operation the left tube and ovary were found to be normal, as was the uterus. An organized blood clot filled the cul-de-sac. The right ovary contained a cyst 2 cm. in diameter which was adherent to the broad ligament. The right tube was distended in the outer third to a diameter of 4 cm. and old blood clot blocked the fimbriated end. Because this was also a sterility case and the inner half of the right tube appeared normal, a simple resection of the right tube together with a resection of the cystic part of the ovary was performed.

The patient made an uneventful recovery from this procedure.

Pathological Report (S50-3070): The resected tube is dark red, distended, with the fimbriated end closed. The mass measures 6 by 4 cm. The cut surface shows the tube to be filled with dark red clot. Microscopic diagnoses were: midproliferative endometrium with tuberculous endometritis; tubal pregnancy, right, intact, with blighted ovum showing necrosis, thrombosis, and hemorrhage; acute and chronic salpingitis; chronic perioophoritis and endosalpingiosis; follicle cyst. Further sections of the tube revealed tuberculous salpingitis and acid-fast stains on the tubal material were positive.

The patient was readmitted on Dec. 4, 1950, for further surgery. At this time laparotomy revealed many fine adhesions around the left tube and stump of the right tube. A complete hysterectomy with bilateral salpingectomy was performed, penicillin and streptomycin being placed in the peritoneal cavity and continued parenterally postoperatively. An uneventful recovery occurred.

Pathological Report (S50-5206): Chronic cervicitis with epidermoid hyperplasia; tuberculous endometritis; 25-day secretory endometrium; tuberculous salpingitis, bilateral.

Comment

The pathogenesis of tuberculous salpingitis has been extensively described[12, 13, 14] and it is not our purpose to discuss this controversial issue at this time. The etiology of tubal gestation similarly is still unsettled, most authors feeling, however, that previous tubal disease of gonococcal or postabortal origin plays the major role in disturbing normal tubal physiology. Tuberculosis has been said to be the etiological factor in approximately 5 per cent of all salpingitides although Hundley[15] in a recent report found tuberculosis in only 1.7 per cent of his cases of salpingitis.

The infrequency of simultaneously occurring tuberculous salpingitis and ectopic pregnancy has never been completely explained. Mann and Meranze[7] noted that the tubal lumen tended to remain open to a slight degree in the early stages of the disease and occasionally also in advanced cases. Frank[13] pointed out that in nearly half the cases the ostium abdominale remains open. Thus the stage is set for the ascent of spermatozoa and since the tuberculous lesion may occasionally be focal, nidation and development may occur. Despite these pathologic findings, Hanson and Rock[16] reported that tubes were found to be clinically occluded in from 33.3 to 80 per cent of cases with salpingographic tests. Sharman[17] noted tubal occlusion in 61.8 per cent of 89 sterility patients having tuberculous endometritis. Greenberg[14] found sterility to exist in 60 per cent of the married patients in the 200 cases of tuberculous salpingitis that he studied and Brack[18] noted a high percentage of obliterated primordial follicles in women who died of pulmonary tuberculosis. It is not known whether this observation connotes a specific primary effect of the disease on the ova with resultant defective germ plasm or whether the follicular disorganization is secondary to the chronic debilitating nature of the illness.

It is our impression that the tuberculous salpingitis-ectopic pregnancy combination is rare because: (1) The disease process is usually bilateral and sterility is a common finding in this group. (2) The necrotic mucosa provides unfit ground for nidation of a "ripe" egg. (3) Insufficient microscopic examination or insufficient blocks may not reveal the typical lesion. In this regard, uterine curettage may be of aid since the lesion (as in our case) may be first detected in the curettings and then multiple sections of the tube prepared. (4) The ovum, possibly trophoblastically inefficient, may be unable to implant. (5) The reported high incidence of tubal occlusion prevents fertilization.

Summary and Conclusions

1. The simultaneous finding of tuberculous salpingitis and ectopic pregnancy is a gynecologic rarity. Forty-one cases have previously been reported in the literature, and the authors add another.

2. The possible etiological factors of this rare combination are discussed.

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ARRHENOBLASTOMA COMPLICATING PREGNANCY

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SINCE Robert Meyer[1] first described the arrhenoblastoma as a pathologic entity, numerous reports of the occurrence of such a tumor have been made. It has been rare, however, for any report to be made in which the arrhenoblastoma coexisted with pregnancy.

Histologically, there have been three general groups into which the majority of arrhenoblastomas may be placed:

1. Those with structures frankly resembling testicular tubules. This group has least often caused changes in the host which could be ascribed to the production of androgenic hormone.

2. Those showing epithelial cords without lumina.

3. Those of a sarcomatoid appearance. This completely undifferentiated type of tumor was most often found when the host revealed changes of a defeminizing, or further, a masculinizing nature.

Those tumors which fail to produce androgenic hormone cause no changes in the host organism and simply exist in the presence of normal female physiology, much as would any other inert ovarian neoplasm. Three such tumors have been reported coexistent with pregnancy.

Felicissimo and Junqueira[2] reported the first case of arrhenoblastoma complicating pregnancy in 1938. The tumor was physiologically inert and was discovered in the fifth month of gestation when symptoms due to torsion of the pedicle occurred.

Recently Dougherty and Lund[3] reported two cases of arrhenoblastoma complicating pregnancy. In neither case were symptoms of a defeminizing or masculinizing nature found.

Those tumors which do produce androgenic hormone cause changes in the host organism which were described by Meyer.[4] Signs of defeminization are supposed to occur first: Anovulation, amenorrhea, breast atrophy, and changes in body contour. Subsequently, true masculinizing features follow. Among these are skin and hair changes, voice changes, and enlargement of the clitoris. If the physiologic effect of the active arrhenoblastoma is as described, it would appear that pregnancy could not occur in the presence of such a tumor. Yet such a case has been reported. In 1945, Brentnall[5] reported the case of a 26-year-old woman in whom a pregnancy and hormone producing arrhenoblastoma coexisted. The physiologic effects of the tumor included acne, marked hirsutism, deepening of the voice, and enlargement of the clitoris. The tumor was removed at the time of delivery by cesarean section and of great interest is the fact that the child was a female pseudohermaphrodite. Brentnall suggests that pregnancy occurred while the tumor was producing very small amounts of hormone, and that the increased pelvic vascularity of pregnancy might have caused the tumor to become more active. Certainly the simultaneous occurrence of pregnancy and an androgenic arrhenoblastoma is most unusual and is the reason for the following report.

V. P., aged 21 years, and nulligravid, was admitted to Harlem Hospital on July 3, 1943, because of lower abdominal pain. The patient gave a history of regular menstrual periods since age 13. There was no history of amenorrhea and her last period was June 15,

1943. On admission, there was noted marked generalized hirsutism in a definite male pattern, moderate deepening of the voice, and marked enlargement of the clitoris with the glans and prepuce well differentiated. There was a tender, somewhat cystic mass lying in front and to the left of the uterus. Nine weeks following admission, laparotomy was performed with the diagnosis of infected ovarian cyst. At operation a large cystic mass was found arising from the right ovary and twisted 360 degrees on its pedicle. Grossly the left tube and ovary were normal. The histologic report was "ovary showing clusters of cells with mitotic figures and anaplasia." A definite diagnosis was not made at the time. The slides were seen by several pathologists, one of whom made the diagnosis of arrhenoblastoma.

The patient was readmitted on March 14, 1944, about 6 months postoperatively, because of enlarging abdomen and abdominal pain. She had menstruated irregularly following operation and had her last menstrual period on Jan. 3, 1944. Examination revealed the presence of ascites and an irregular pelvic mass. There had been no change in voice, hair distribution, or clitoral size since the previous admission. At operation, 2,200 c.c. of greenish-yellow fluid were found in the peritoneal cavity. A mass arising from the left ovary was found. It measured 15 by 15 cm. and was semisolid. A left salpingo-oophorectomy was done. The uterus was the size of a 14 weeks' gestation. The day following operation, the patient aborted a 12 weeks' fetus. Histologic diagnosis at this time was arrhenoblastoma of the ovary.

The patient failed to return to the clinic and the interim history was obtained from her family physician. "There was a marked diminution in hirsutism, diminution in the size of the clitoris, and the onset of menopausal symptoms. The general condition was good."

In October, 1948, five years following the first laparotomy and four and one-half years following the second, the patient was admitted to another city institution with a diagnosis of incarcerated omental incisional hernia. At laparotomy a mass 6 by 8 cm. was found in the old scar lying between the rectus muscle and the fascia. There were a few intestinal adhesions but no pelvic masses and no palpable lymph nodes. The uterus was small and atrophic. On the right lobe of the liver two small nodules were palpated. Pathological diagnosis at this time was "second degree granulosa-cell tumor of the abdominal wall and liver."

The patient was readmitted to Harlem Hospital on Oct. 1, 1949, because of a persistent cough. X-ray of the chest revealed bilateral cannon-ball lesions. There were no bony metastases found. Deep x-ray therapy was given to the chest and pelvis and the patient was discharged on Feb. 19, 1949.

The last admission of V. P. occurred on Feb. 27, 1950, because of severe right lower extremity pain and foot drop. Her condition deteriorated progressively and the patient died on April 11, 1950, not quite seven years after her first hospital admission. At autopsy metastatic lesions were found in the brain, lungs, mediastinal lymph nodes, and liver. The uterus was small and atrophic and there were no intraperitoneal or abdominopelvic lymph node metastases.

The histologic diagnosis was metastatic arrhenoblastoma, and this has been registered with the Ovarian Tumor Registry, Case No. 45.

Comment

It is probable that the tumor found in the left ovary was present at the first laparotomy performed six months previously. However, it undoubtedly was small enough to be undetected grossly. Pregnancy did occur following removal of the larger tumor with its androgenic capacity. Following Bretnall's hypothesis, pregnancy may have occurred while the second neoplasm was comparatively inert and the increased pelvic vascularity caused by pregnancy may have aided in the rapid growth of this tumor.

Summary

1. A case of malignant arrhenoblastoma with masculinizing symptoms coexisting with pregnancy is reported.

2. Four previous reports of arrhenoblastomas complicating pregnancy are reviewed, only one of which included a tumor that was physiologically potent.

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STROMAL MYOSIS*

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STROMAL myosis, or endolymphatic stromal myosis,[1] is a type of uterine neoplasm characterized by the microscopic picture of cells resembling endometrial stroma which invades the myometrium in bundles and cords, along perivascular and perilymphatic spaces, within the lumina of the lymphatics and occasional blood vessels. This subject was thoroughly reviewed by D. N. Henderson.[1]

In 1948 Park and Tennent[2] reported such a case which they called stromal endometriosis. In this case there were fingerlike extensions into the base of the right broad ligament to the pelvic wall, and into the upper part of the right broad ligament to a point just below the ovarian vessels. In August, 1950, Da Cunha[3] reported a similar case with extension into the right broad ligament to the lateral pelvic wall. He tells of W. W. Park's analysis of the 50 reported cases of stromal endometriosis; of the 43 patients fully followed up 5 died as a direct result of the disease. In 2 cases reported by Goodall metastases were found in the lungs; in five other cases local recurrence of neoplasm occurred.

Mrs. B. M., a 40-year-old white, gravida i, para i, was admitted to Michael Reese Hospital Aug. 12, 1946, because of profuse menstruation accompanied by the passage of large clots, lasting 10 days. For the past two years her menstrual periods had been irregular, occurring at 2- to 8-week intervals. Her menarche occurred at 14 years, with a 28-day cycle, and a 7-day flow. The past history is negative except for an operation five years before consisting of a Manchester plastic, anterior and posterior colporrhaphy. Sixteen years before she had a normal full-term delivery with low forceps and episiotomy. Her general systemic complaints were negative except for frequency of urination of one year's duration. The family history was nonessential.

Physical examination revealed a well-nourished, well-developed woman who appeared to be in good health. Her weight was 140 pounds, the blood pressure was 120/80. On palpation of the lower abdomen a firm, tender, freely movable mass was felt behind the symphysis pubis. Vaginal examination revealed a multiparous introitus, external genitals were normal, there was slight relaxation of the pelvic floor; the uterus was hard, irregular, freely movable and enlarged to the size of a twelve weeks' pregnancy. Speculum examination revealed a normal cervix. The red blood count was 3,800,000, hemoglobin 78 per cent, urine normal, Wassermann negative.

Operation consisted of vaginal hysterectomy, resection of a cyst of the left ovary, and perineorrhaphy. The uterine mass was delivered by excision of the corpus from the fundus of the uterus and delivery of the remainder by morcellation. The nature of the pathology was unsuspected at the time of surgery.

The postoperative course was uneventful until the seventh day when the patient developed cystitis which cleared up with sulfathiazole and sulfadiazine therapy. On the eighth day an x-ray of the chest was taken which revealed no evidence of pulmonary metastases. On the tenth day deep roentgen therapy was begun. On the eleventh day 500 c.c. of fresh whole blood were given because the red blood count had dropped to 2,900,000, and hemoglobin to 50 per cent. The patient was discharged on the twelfth day, but returned to the hospital daily until 8,000 r had been given through an anterior and a posterior portal.

The pathologist describes the myometrium as being very thick, gray pink, streaked and studded with gray-white areas. In sections of the uterus stained with hematoxylin and eosin in one field proliferating endometrium is seen to be stretched over a cellular mass which

*Presented before the Chicago Gynecological Society, Nov. 17, 1950.

apparently derives from the stroma and extends into the underlying myometrium. This mass is composed of spindle-shaped cells with fairly uniform oval or elliptical nuclei. The chromatin content of the latter varies somewhat and mitotic figures are scattered sparsely throughout. The cytoplasm of the cells is negligible and lightly eosinophilic. Within the

Fig. 1.

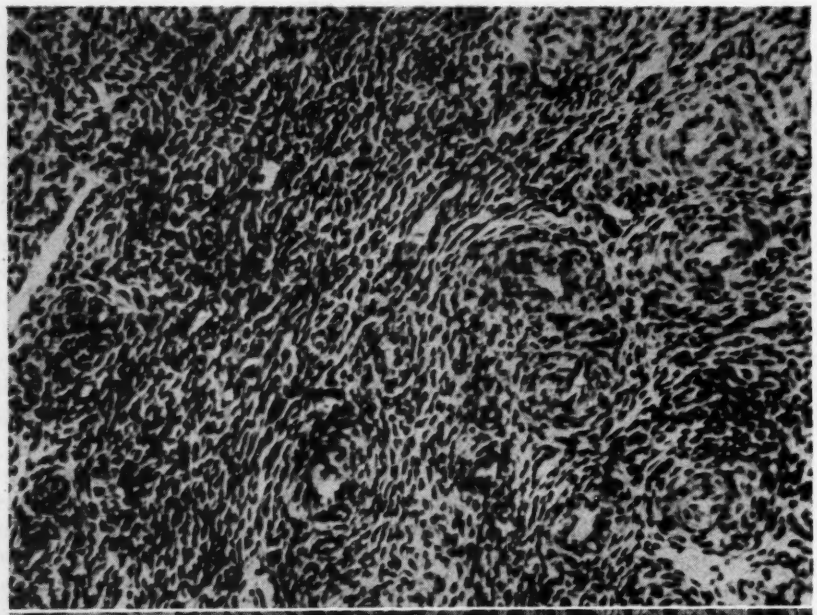

Fig. 2.

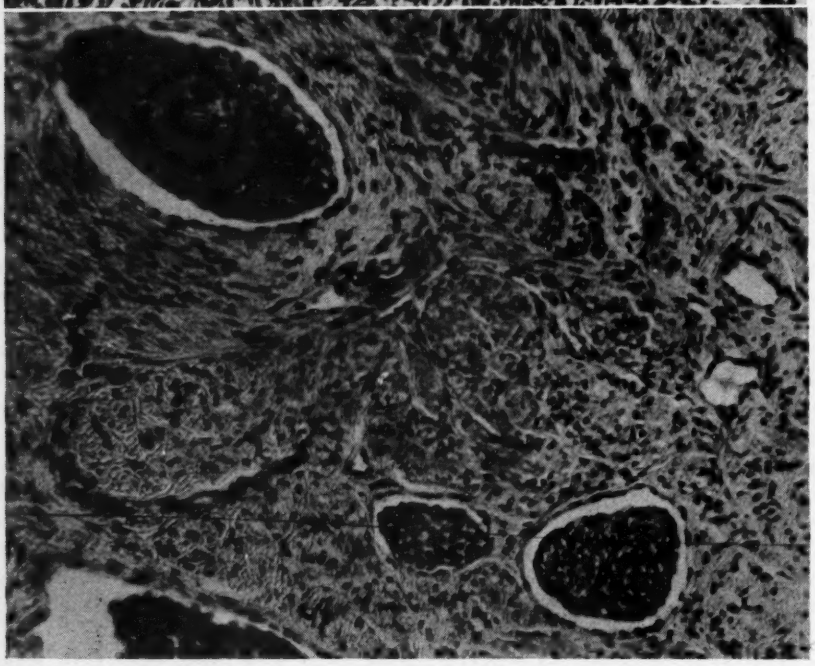

Fig. 1.—General appearance of most of the abnormal tissue which involved all of the uterine wall. (×100.)

Fig. 2.—Tumor cells within an endothelium-lined space. (×100.)

masses vascular channels are noted. The contained blood vessels vary somewhat in thickness but are not larger than arterioles in dimension. Free within the lymphatics and vascular channels of the myometrium are similar circumscribed masses.

Fig. 3.

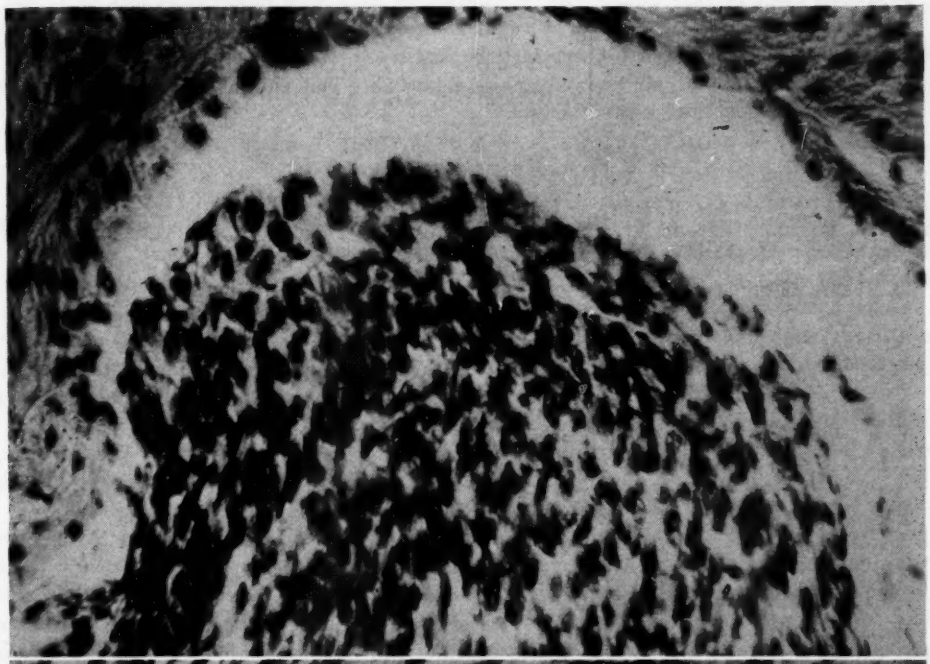

Fig. 4.

Fig. 3.—Tumor cells growing into lumen of an endothelium-lined channel. (×400.)
Fig. 4.—Tumor cells within an endothelium-lined channel. (×400.)

Comment

Stromal myosis is not as benign a condition as one may have gathered from previous reports, since the mortality is 11 per cent and rate of recurrence 23 per cent in the 43 cases reported with full follow-up.

Prognosis must be very guarded since recurrences have been reported as late as 17 years.

These patients must be checked at regular intervals so that at the first sign of recurrence early surgical or roentgen therapy may be instituted.

An additional case of stromal myosis is reported. The patient is free of recurrence four years after surgery and x-ray therapy.

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RADIATION EFFECT ON THE UNBORN EMBRYO IMMEDIATELY AFTER CONCEPTION

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WITH the more extensive use of roentgen irradiation in the treatment of certain sterility cases with amenorrhea or anovulatory menstruation, the hazards to the progeny of the first or second generation must be considered. The data obtained from animal and insect experimentation cannot be applied directly to human beings.

Since the "Committee on Atomic Casualties" has stated that most mutations in animals are recessive, only the small proportion of mutations that are dominant may be expected to show genetic effects in the first postirradiated generation.

Radiation experiments on human reproductive organs are impossible. When an "experiment" occurs accidentally, observations and conclusions based upon it are important to record.

A clinical experiment was afforded by the following case: B. E., a 24-year-old white woman, nulliparous, was first seen on June 20, 1949, with a history of infertility of two years' duration. Her past history was insignificant except that her menstrual cycles were irregular. They occurred from four to nine weeks apart and lasted three to four days with no dysmenorrhea. Her menarche started at the age of 14 years. She had the usual childhood diseases without complication, and there were no serious illnesses and no operations.

On physical examination she appeared to be very slim, with underdeveloped, conical breasts, and flat nipples. Hair distribution was normal. The heart and lungs were normal and blood pressure 110/70. Pelvic examination revealed the vulva to be slightly underdeveloped with nulliparous introitus. Speculum examination revealed the cervix to be long and narrow with pinpoint cervical os, and facing posteriorly. Bimanual examination showed the uterus to be very small, smooth, and anterior. The adnexa were negative. The laboratory findings were as follows: Urine negative; red blood cells 4.3 million; hemoglobin 12 Gm.; white blood cells normal; sedimentation rate normal. The basal metabolism was plus 5 per cent. A tubal insufflation test showed questionable patency but a hysterosalpingogram showed both tubes to be patent. An endometrial biopsy, on the twenty-seventh day of the cycle showed persistent follicular phase. The basal body chart for several months confirmed the presence of anovulatory cycles.

The patient was placed on cyclic therapy because of hypoplasia and after three months' therapy the uterus enlarged to normal size. Menses became regular, occurring every 28 days, but the cycles continued to be anovulatory. She was then placed on pregnant mare serum, 500 units every day for 9 days, followed by chorionic gonadotrophin, 500 units every day for 9 days. This produced no change in the endometrium, this being confirmed by several endometrial biopsies. The patient was then given progesterone, 20 mg. from the twentieth day of the cycle for 5 days. This, too, had no effect. It was then decided to give x-ray stimulation to the pituitary. She received the following radiation to the pituitary: From June 8, 1949, to July 5, 1949, she was given 600 r to the left side of the pituitary and 600 r to the right of the pituitary in divided doses. She was followed for the next six months with endometrial biopsies and basal body temperature charts, but no change of endometrium was noticed. She continued to have a persistent follicular phase. The patient was then advised to have small x-ray stimulating doses to the ovaries. She

was warned not to conceive during the period of therapy. On Jan. 18, 1950, she was given 100 r to the left pelvic region and 100 r anteriorly to the right pelvic region. On Jan. 25, 1950, she was given another 100 r posteriorly to the right and 100 r to the left pelvic region, both with 200 kv. units and 10 by 12 portals. When the patient returned for her third and last treatment, she stated that she was several days late. Her last menstrual period was on Dec. 25, 1949. It was decided not to give her any further radiation due to the possibility that she might have become pregnant in the interval. She admitted that she used no contraceptives. An Aschheim-Zondek test was positive.

The question was debated as to whether this patient be allowed to go through with this pregnancy since she received so much irradiation to the ovaries during the early gestation period. The possibility of an abnormal baby was explained to the patient and her husband. As they were very anxious to have a child it was decided to allow her to go to term. She was treated with endocrines to prevent a spontaneous abortion, this therapy being based on the observation that abortion occurs in about 20 per cent of the cases of primary sterility. At the end of 9 months the patient went into labor after having had a normal prenatal course with active fetal movement from 4½ months on to term. She had a normal labor and an uncomplicated delivery. She was delivered of a normal male baby who cried spontaneously. Thorough examination of the infant revealed a perfect, normally developed child. At the last examination of the baby at six months, there were normal growth and development.

Comment

The subjecting of the very early embryo to radiation therapy because of the patient's conception contrary to instructions produced a grave situation. Our choice was either to perform a therapeutic abortion and so avoid the birth of a possible monstrosity, or to permit pregnancy to proceed, since it had never been shown that such a "small" amount of radiation was harmful to the human embryo.

The patient received 200 r to each ovarian region. With a 200 kv. unit the depth doses at the level of the internal genitals is 30 per cent or 60 r to each ovarian region. The portal of 10 by 12 allowed an area of 3 cm. in the midline which was screened off. Since the embryo was developing in the uterus, which is in the midline and the uterine cavity is 3 cm. in width, the embryo was protected from direct irradiation and the amount from back scatter would be in the neighborhood of 18 r.

In the usual gastrointestinal series and barium enema diagnostic examinations, the uterus is exposed to about 60 r. There have been many such studies carried out in early pregnancy with no evident mutation effect on the fetus. Although Kaplan performed an x-ray therapeutic abortion in a case which had similar therapy to ours we felt that the evidence that mutations may affect the fetus after this dosage of radiation were not conclusive enough to justify an interruption of pregnancy in a sterility case.

Summary

A case in which stimulating doses of x-ray to the ovaries were given in the first 2 weeks of pregnancy is reported. The pregnancy was allowed to go to term and a perfectly normal living infant was delivered.

Comment

By Ira I. Kaplan, M.D., New York, N. Y.

Roland and Weinberg present a very important and momentous report on the birth of a normal baby following x-ray irradiation of the mother apparently when conception had already occurred.

There have been a number of cases reported where pregnancy had proceeded normally even during the course of irradiation for cancer of the cervix, but, up until now, no one had

reported on a case of sterility in which pregnancy was permitted to extend full term with the birth of a normal child, when irradiation had been administered at the time of inception of the pregnancy.

During the past 26 years I have treated more than 425 married women with x-ray therapy for relief of sterility. During this period only one abnormal child was born, and in my report on this case in 1931 I stated it was my belief that the abnormality occurred because irradiation was possibly administered, unknowingly, just after conception had taken place.

Since then I have reported on three cases where therapeutic abortion was advised because of the fear of the birth of an abnormal child, because pregnancy was noted so close to the period of irradiation as to presuppose the probability of irradiation being delivered to the embryo fetus at or too close to the actual conception time.

The report of Roland and Weinberg of a normal child born under similar circumstances indicates that our fear of untoward effects of irradiation at conception time may not be entirely correct.

Evidently, an early embryo is not as sensitive to the x-ray dosage used in the treatment of sterility as has been supposed.

If, subsequently, other cases are reported to occur in the same manner, we can more confidently use irradiation for sterility, which in my hands has proved so consistently successful over a period of 26 years.

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SPONTANEOUS RUPTURE OF THE LIVER IN A PATIENT WITH NONCONVULSIVE ECLAMPSIA

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"Spontaneous rupture" of the liver is a rare condition, and that complicating pregnancy is even less frequent. To date, nine cases of rupture associated with pregnancy have been reported.[1-9] Only three of these patients survived, due to prompt surgical interference.[5, 6, 9] An additional case is reported here. It is our impression that the symptoms associated with this complication are sufficiently characteristic to be recognized if the entity is kept in mind.

E. E., a 34-year-old white woman was in the thirty-eighth week of her sixth pregnancy. The previous pregnancies had all occurred in the preceding nine years, but two of them (the second and fifth) resulted in spontaneous abortions in the second and third months, respectively. When she was first seen during the present pregnancy, examination of the patient was essentially negative except for a blood pressure of 162/100. The urine was entirely negative. Though the patient was Rh negative, no antibodies were found in the blood serum and none developed during the following months. In addition to the usual calcium, iron, and vitamins, she was placed on an increasing stilbestrol dosage following the schedule of the Smiths. During the first trimester the pregnancy was uneventful. Then her blood pressure gradually increased to reach 180/120 by the thirtieth week. Slight edema appeared about the ankles and hands by the twenty-sixth week, associated with slight dyspnea, but no headache or other subjective symptoms. The urine showed a small amount of albumin. She was placed on ammonium chloride, phenobarbital, and a low caloric diet with a high protein content, which she followed with irregular degrees of faithfulness. Magnesium sulfate was given orally twice daily. In the thirty-first week of pregnancy, the urine was found to contain 4 plus albumin, many hyaline and granular casts, several waxy casts, few erythrocytes, and innumerable leucocytes. The blood pressure was then 260/140.

She was admitted to Centinela Hospital complaining of severe headache and epigastric pain. Except for the urinary findings, the hypertension, and the enlarged uterus consistent with a gestation of 31 weeks, no additional information was elicited by history or physical examination. The liver and spleen were not palpable. The fundi of the eyes were essentially negative. There was no coma. The patient was mentally alert. In the hospital she was given hypertonic glucose and magnesium sulfate intravenously, and sedation. The blood pressure soon fell to 158/118 and the epigastric pain disappeared. Eight hours later the blood pressure again rose to 260/180.

The morning of the second day the cervix was found to be 4 to 6 cm. dilated, so she was moved to the delivery room where the membranes were quickly ruptured and the patient put to bed. While she was on the table, it was noted that her blood pressure had dropped to 180/140, later falling to 120/0. When she was returned to bed, no pressure could be determined, and she was practically pulseless, but remained conscious up to the time of her death. Despite intensive supportive therapy, she died less than 48 hours after her admission to the hospital.

Autopsy Findings.—The body was that of a moderately obese, well-developed woman, measuring 65 inches in length and weighing approximately 140 pounds. The breasts were

symmetrical, enlarged, and showed evidence of lactation. The abdomen was protuberant due to pregnancy. The skin was pale and no edema was noted in the extremities.

When the abdomen was opened, the liver was found to be greatly enlarged, weighing approximately 4,000 grams. A large hematoma was present below the capsule over the entire anterolateral portion of the right lobe extending from the inferior margin up to the dome. A 9-cm. laceration was present in the capsule through which the hematoma partially extruded. The parenchyma was soft, the cut surfaces bulged and presented a mottled yellow to orange-brown discoloration with many areas of hemorrhage. About 700 c.c. of clotted blood were present in the peritoneal sac. The kidneys were moderately enlarged, each weighing approximately 200 grams. The capsules stripped with difficulty causing small lacerations of the kidney surface. The kidney parenchyma was pale, somewhat mottled, and the cortex was thickened. The uterus was enlarged and contained an 8-month, well-developed fetus. Numerous small myomas were present in the myometrium. Examination of the fetus revealed nothing remarkable except for generalized cyanosis and numerous small hemorrhages over both lungs consistent with asphyxial death. The placenta was tightly adherent to the uterine wall but otherwise appeared normal. The heart weighed approximately 420 grams and the left ventricular wall measured 2 cm. in its greatest diameter. Examination of the remainder of the viscera revealed nothing remarkable.

Microscopic examination of the tissues revealed marked acute hepatic necrosis with extensive parenchymatous hemorrhage typical of the changes seen in eclampsia. The kidneys revealed a moderate arteriosclerosis with scarring of the cortex. Changes seen in the other organs were not significant.

The cause of death was classified as follows:

1. Nonconvulsive eclampsia gravidarum.
2. Acute hepatic necrosis with subcapsular hemorrhage and spontaneous rupture.
3. Intraperitoneal hemorrhage with shock.

Comment

There have been nine reports of patients with spontaneous rupture of the liver complicating pregnancy.[1-9] Our case report makes the tenth. The condition was not suspected or diagnosed prior to death or operation in any of the patients. In three, however, because of signs of shock, intra-abdominal hemorrhage from an unknown source was suspected so that patients were operated upon, the hemorrhage from the liver controlled, and the patients recovered. It would appear, then, that surgery would be the only hope for survival in such patients, provided the pregnancy was terminated.

Right upper quadrant or epigastric pain, which appears to be a constant finding and perhaps a characteristic feature, is probably due to the liver damage and/or the subcapsular hepatic hemorrhage. This, associated with signs and symptoms of toxemia or eclampsia, followed by signs of shock and peritoneal hemorrhage, apparently completes the symptom complex of the entity.

It is quite likely that parenchymatous necrosis is the major factor that underlies the hemorrhage. The hemorrhage may be initiated and further assisted in its extent by both the hypertension and trauma of any degree. Our case and several of the others suggest that the hemorrhage developed first under the capsule which subsequently ruptured to allow peritoneal extravasation. The trauma associated with convulsions could well be the traumatic factor in these patients, but convulsions were present in only three of the reported nine cases. External trauma, such as moving the patient or pressure on the abdomen of any type, would serve a similar purpose, and could well escape notice as an etiological factor. With the exception of one case, no history of such trauma was recorded. Increased intra-abdominal pressure associated with vomiting or labor could also be the basis for the traumatic factors. In the patient reported by Sames and Kaminski, the symptom complex developed after a strong sustained contraction of the uterus following the administration of Pitocin.

Summary and Conclusion

The tenth case of reported spontaneous rupture of the liver with intra-abdominal hemorrhage complicating nonconvulsive eclampsia was described.

The cause of hemorrhage is probably the hepatic necrosis assisted by the hypertension and complicated by trauma, such as palpation of the abdomen, convulsions, vomiting, labor, or moving the patient.

In most of the cases, the hemorrhage was first subcapsular probably accounting for the right upper quadrant and epigastric pain.

Three of the ten patients survived due to surgical intervention. The only hope for survival in these patients is the recognition of the complication and its symptom complex followed by surgery.

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Selected Abstracts

Analgesia, Anesthesia

Pellizzari, C.: Intravenous Novocain During Labor for Analgesia, Riv. ital. di ginec. **34:** 104, 1950.

The author has used Novocain during labor in 30 cases, obtaining results not as good as those claimed by other obstetricians. He has used solution of 5 per cent glucose with from 0.6 to 2 per cent Novocain by the drip method, giving from 1 c.c. to 4 c.c. per minute, according to the character of uterine contractions. This method gave good analgesia in only a limited number of patients. A marked relaxation of the cervix and perineal floor was obtained, but analgesia was seldom effected. The action was very like that of a narcotic. In the cases cited there were no maternal or fetal complications. RINA D'AMICO

Casabona, U., and Giotto, B.: Combined Saddle Block and Medical Management of Labor, Minerva ginec. **10:** 411, 1950.

Saddle block analgesia, introduced in obstetrics by Parmley and Adriani in 1946, is very effective, but necessitates operative delivery in 45 per cent of cases, due to inertia. The authors have used the saddle block together with the Theobald-Graham medical treatment and have obtained very satisfactory results. For the saddle block they have used 2.5 mg. or 5 mg. of Nupercaine (Ciba) by intrathecal injection, obtaining analgesia which lasted from 3 to 6 hours. The medical treatment was started at the beginning of the second stage and consisted of 250 c.c. 5 per cent glucose with 5 units of Pitocin. The solution was given at a rate of 12 to 15 drops per minute and was discontinued soon after the third stage.

The patient was asked to collaborate by bearing down at the right time and she was able to do well. Blood pressure was taken frequently and when necessary ephedrine or Sympatol was used. Headache due to the intrathecal injection was observed in 17.5 per cent of cases, being mild and of short duration. The authors believe this is the best method of analgesia to be used by specialists in hospital practice. RINA D'AMICO

Cancer, Malignancies

Brown, Willis E., and Jernigan, George C.: Carcinoma of the Cervix in Pregnancy, The American Surgeon **17:** 441, 1951.

In a series of 9,056 deliveries at the University of Arkansas Hospital there were 19 cases of carcinoma of the cervix which were diagnosed. The incidence of cervical carcinoma complicating pregnancy was 1 to 477. The diagnosis of intraepithelial carcinoma in pregnancy is fraught with grave danger. A case is reported of a woman 38 years of age, pregnant for the first time, in whom a biopsy of a cervical erosion was reported by the pathologist to show intraepithelial carcinoma. As the pregnancy progressed, no evidence of invasive carcinoma appeared and at 12 weeks post partum the cervix was amputated and extensive and numerous sections were made. No evidence of invasive carcinoma was found and intra-

epithelial carcinoma could not be demonstrated. Many biopsies taken on pregnant women reveal tissue changes sufficiently anaplastic to be classified as carcinoma in situ. Hyperactivity of the basal layers of epithelium is a common finding and may be confusing. It is well known that carcinoma-like histologic changes may develop in the pregnant cervix which are indistinguishable in their anaplastic appearance from true carcinoma. These abnormal cell patterns revert to normal following delivery.

Clinical carcinoma of the cervix does occur during pregnancy and in most patients the lesions are in the early stage. This is probably explained on the basis that more advanced lesions render the patient infertile. The treatment of carcinoma of the cervix in pregnancy follows the general principle of x-ray, radium, and surgery in accordance with the stage of the disease and the treatment program is not necessarily altered by the pregnancy. Spontaneous abortion practically always occurs following the irradiation and presents no problem. Occasionally the treatment program may be modified in late pregnancy to permit fetal viability before full radiation is applied. WILLIAM BICKERS

Loeser, A. A.: The Combined Action of Male and Thyroid Hormones on Cancer of the Female Breast and Genitals, Gynécologie Pratique 1: 179, 1950.

Loeser, of London, summarizes 13 years of experience with male and thyroid hormones and their effects on selected cancer cases before the International Congress on Cancer held in Paris, July 18, 1950. In 1937 the author initiated his studies on two cases of breast carcinoma injected with massive doses of testosterone propionate. He states that while his work was confirmed by others no permanent control or cure of breast cancer has been attained.

Since massive doses of male or female hormone cause a derangement of the metabolism by blocking all the tropic hormones of the anterior pituitary, especially the thyrotropic hormone, a special type of hypothyroidism develops. The normal cell metabolism in the cancerous body may be damaged and thus its "resistance" against latent or active cancer cells is reduced. Because of these reasons the author, in nine cases of cancer (one endometrial, one ovarian, and seven breast carcinomas), has injected thyroxine and testosterone either into the tumor itself or near by. Four out of 6 breast cancer cases which had been inoperable and hopeless before treatment became operable. The removed breasts were examined microscopically and the effect of testosterone and thyroxine on the cancer cell was studied. Biochemical investigations (cholinesterase and the androgen-estrogen ratio in the urine) were made in all cases.

Loeser concludes that thyroid hormone has in many cases inhibited masculinization brought about by massive doses of testosterone (3.0 to 3.6 grams annually). Testosterone, together with thyroid hormone as a catalyst, influences the cancer cell itself better than testosterone alone. Some inoperable cases can to a certain extent be rendered operable by the combined action of these two hormones. Permanent application of thyroid after operation is advisable for maintenance of normal metabolism. The nine case reports are included. CLAIR E. FOLSOME

Gynecology

Leroux, M., and Guiheneuc, B. O.: First Results From Streptomycin Therapy in Tuberculosis of the Female Genitals, Gynéc. et obst. 49: 479, 1950.

The authors, from Nantes and Rennes, summarize three years' experience with the use of streptomycin in tuberculosis of the female pelvis. It was employed in 100 such cases (1 case of vulval, 2 cases of cervical, 15 cases of endometrial, and 92 cases of adnexal tuberculosis).

The single case of primary tuberculosis of the vulva, proved by biopsy, was treated with 0.5 Gm. daily for six weeks. The lesion receded and was cured. The single case of cervical tuberculosis was treated 63 days with a combination of penicillin, x-ray, and streptomycin. The 15 cases of endometrial tuberculosis were associated with tuberculosis elsewhere in the

pelvis. The 92 cases of adnexal tuberculosis were distributed as follows: 23 with the miliary ascitic form; 43 cases of the simple peritoneal-adnexal type; 14 cases of peritoneal-adnexal type with fistulas; 7 cases were associated with other localized tubercular processes; 1 case was with pregnancy; and 4 cases could not be accurately classified. The ascitic-miliary form responded most rapidly to streptomycin treatment. Incomplete results were obtained in 3 cases. There were excellent results in 23 cases without surgical intervention, and 17 cases were treated successfully by a combination of streptomycin and pelvic exenteration.

The authors conclude that streptomycin is the treatment of choice in tuberculosis of female genitals. In some it apparently arrests the process, in others surgery is made much simpler with adequate pre- and postoperative use of streptomycin. While streptomycin did provoke several rare toxic reactions, the writers agree these should not deter its judicious use.

CLAIR E. FOLSOME

Ishizuka, Naotaka: Artificial Corpora Lutea in the Human Female, M. J. Osaka University **2**: 103, 1950.

A trophoblasthormone was made from human placental tissue or hydatid mole by means of acetone-benzoic acid extraction. The solution obtained was colorless with a pH of 5.8 to 6.0. It could be injected into human beings without adverse generalized body reaction. The strength of the solution was determined by the induction of follicle bleeding in a rabbit, a unit being taken to be the minimal amount required to cause follicle bleeding 48 hours after one subcutaneous injection. In 9 patients with carcinoma of the cervix, treated with various dosages and at various times with trophoblasthormone, follicle bleeding was instituted in 6, and luteinization of the theca cells occurred in 3. The author estimated that it was necessary to inject 150 units or more to obtain follicle bleeding. He was unable to induce luteinization of the granulosa cells and ovulation did not occur. LOUIS M. HELLMAN

Whitelaw, M. James: Ovulation After Unilateral Oophorectomy as Determined by Endometrial Biopsy and Basal Body Temperature, Surg., Gynec. & Obst. **92**: 747, 1951.

In an attempt to study ovarian function after removal of one ovary the author has studied 42 women, all under 30 years of age, who had had one ovary removed eight or more months prior to the investigation. Although there were no control studies on these individual patients, a group of a like number of postpartum patients under 30 years of age was selected at random. One hundred sixty-eight biopsies were done on the 42 women who had been operated upon, covering four consecutive cycles. The author was unable to show any difference in the endometrial pattern of the women who had had one ovary removed as compared with the control group. In the total series of 350 biopsies, slightly less than 0.9 per cent showed an anovulatory cycle. There was no difference between the control group and the group of women who had been operated upon. LOUIS M. HELLMAN

Gynecologic Operations

Vecchietti, G.: A Simple Method of Extramucosal Perineoplasty, Minerva ginec. **10**: 422, 1950.

The author describes a personal method of perineoplasty used with excellent results in 42 women. He claims that it is very simple and efficacious in patients with a small perineum due to previous lacerations and before complications of cystocele and rectocele. After a description of the anatomical-pathological alterations, there follows a detailed explanation of the technique, illustrated by some schematic drawings. The new technique consists of building up of the pelvic floor without touching the vaginal mucosa, but reaching the perineal muscles through an opening in the region between the vulva and the anus. RINA D'AMICO

Labor, Management, Complications

Burton-Brown, Jean R. C., and Shepherd, John A.: Rupture of the Liver Associated With Parturition, Brit. M. J. 1: May 28, 1949.

The authors review reports in the literature of three cases of rupture of the liver in pregnancy and add a fourth case. The authors' patient recovered following laparotomy and control of bleeding with oxidized gauze. They suggest that their case was associated with trauma produced by violent contractions of the diaphragm and abdominal muscles. There was an element of toxemia which may have rendered the liver more susceptible to injury. They suggest that liver ruptures be divided into two groups: traumatic (in a normal liver) and hepatic apoplexy (secondary to hemorrhage in a pathological liver). DONALD G. JOHNSON

Dumont, Martial: Study of Labor in Primipara Previously Operated Upon, With Success, by Presacral Nerve Resection for Relief of Dysmenorrhea. Analysis of 38 Cases, Gynéc. et obst. 50: 35, 1951.

Dumont, from the Obstetrical Clinic of the Lyon Medical School, observed in considerable detail the type of labor, its duration, and the degree of labor pains in a series of 38 primiparas who had previously undergone presacral nerve resection for the successful relief of pre-existing dysmenorrhea.

Dumont found the duration of the first stage of labor diminished. It was less than 11 hours in 81 per cent of the cases. The second stage was no different than that in the control series. The total duration of labor was greatly decreased, less than 12 hours in 73 per cent of the cases. The mechanics of delivery caused no problem. In 16 per cent of the series the first stage was painless and in 60 per cent the pain was but slight, or in a total of 76 per cent of the cases there was decreased or no pain in the first stage of labor. Pains during the second stage, however, were similar to those of the normal primiparous second stage of labor. CLAIR E. FOLSOME

Menstruation

Vignes, Henri: Influence of Menstruation Upon Skin Diseases, Gynéc. Pratique 1: 219, 1950.

Vignes, of Paris, notes that the skin of women is influenced by their menstrual cycle but that these responses are usually imperceptible to them. The vasomotor system is influenced via the parasympathetic pathway, making the susceptibility of these end organs more responsive to stimuli.

Menstruation modifies the sweat, including an elevation of the choline and creatine values during menses. The author mentions others who describe a typical cycle for the sudoriparous glands of the axilla which is synchronous with the menstrual cycle. The catamenia frequently provokes or exacerbates certain types of cutaneous disorders, including acne, premenstrual erythemas, catamenial eczemas, seborrhea, herpes, pigmentation, pruritus, urticaria, and psoriasis; anal fissures are made worse at time of menses. Vignes concludes that while we are aware of these clinical facts we must be careful in our evaluation for interpretation is hazardous. The therapeutic results from use of endocrines versus usual cutaneous therapy are, at times, curiously contradictory. Some hormones which may be considered as antagonists may actually produce successful therapy. CLAIR E. FOLSOME

Swyer, B. I. M.: Oral Hormonal Therapy for Menstrual Disorders, Brit. M. J. 1: 626, 1950.

The author reports on 52 patients complaining of menstrual disorders. They are grouped into cases of (a) prolonged and excessive bleeding with irregular cycles; (b) excessive bleeding with regular cycles; (c) cases of scanty infrequent anovulatory cycles, and (d) cases of secondary amenorrhea. The author's regimen of therapy consists of administration of

stilbestrol in a dose of 2 to 5 mg. daily for the control of bleeding. Once this is achieved, 2 mg. daily are administered for 20 days. The next cycle, stilbestrol alone, is given for 20 days, whereas in the following 3 cycles stilbestrol and anhydrohydroxy progesterone are given as follows: 2 mg. stilbestrol are given daily for 20 days starting on the fifth day of the cycle, and from the fifteenth day of the cycle 20 mg. of anhydrohydroxy progesterone are given daily for 10 days. For the fifth cycle, the dose of stilbestrol is reduced to 1 mg. daily and that of anhydrohydroxy progesterone to 30 mg. For the sixth cycle, the daily doses are 0.5 mg. and 40 mg. respectively.

The aim of therapy is to produce ovulation. The author states that there seems to be good reason to conclude that the administration of estrogen and progesterone has an action on the pituitary gland, causing the latter to function in the manner necessary to determine ovulation.

The treatment appeared to be responsible for re-establishment of ovulation in at least 15 out of 30 patients (not including cases of secondary amenorrhea and menopausal menorrhagia) in whom failure of ovulation had been presumed or proved. Pregnancy occurred in 6 patients.

WILLIAM P. GIVEN

Miscellaneous

Dumont, Martial, and Ricard, Andree: Histindinuria in Serious Pathology, Gynéc. et obst. **50:** 71, 1951.

The authors ran urinary histidine determinations upon 64 cases. This series included the following number and types of cases: 5 cases of serious nephropathies; 5 cases of hydatidiform mole; 11 cases of primary inertia; 21 cases of placental retention; 20 cases of threatened abortion; 1 case each of ectopic pregnancy and placental polyp.

The histidine test in urine was more frequently negative in pre-eclampsia and its absence suggests that condition. The histidine test was positive in hydatidiform mole and negative in primary uterine inertia. The authors feel the Kappeler-Adler hormonal theory explains increased histidinuria by the inhibition of hepatic histidase through the action of the placental hormones. The histidine test seemed to offer no value in the differential diagnosis of threatened abortion and postabortal placental retained fragments. CLAIR E. FOLSOME

Mandy, Arthur J., Farkas, Robert, Scher, Ernest, and Mandy, T. E.: The Natural Childbirth Illusion, South. M. J. **44:** 527, 1951.

The program of natural childbirth advocated by Grantly Dick Read is challenged on several important points. It is doubtful whether active participation of the patient during childbirth is necessary for the satisfactory completion of normal labor. The widespread use of analgesia and anesthesia during recent years has been associated with an ever-decreasing maternal and fetal mortality. The rationale for his preliminary training routines are open to question and the entire theory of "fear, spasm, and pain," founded on a hypothetical description of the pain mechanism in labor, exposes the entire program to question. His anthropologic and psychiatric speculations are premature and unproved. It must be remembered that the program was developed in England where relatively few of the mothers receive pain-relieving drugs during labor and the personal charm of Dr. Read undoubtedly brought assurance and confidence to patients who otherwise would have been highly sensitive to the pain stimuli of labor. A moderate degree of discomfort can be magnified by fright and fear of the unknown.

Read has referred frequently to the ease with which primitive women bear their children, but statistical information along this line does not support this thesis.

It is the opinion of the author that the success of the Read program can be traced to hypnosis in his patients. Read denies this as the means by which relaxation is obtained, but his program can scarcely be separated from the technique of hypnosis. There is no doubt that

Read brought forcefully to the attention of the profession a neglected therapeutic aid in the management of labor. The establishment of a good relationship based on confidence between doctor and patient can aid in all physiologic processes and more especially in that of parturition. WILLIAM BICKERS

Newborn

King, Earl B.: The Placental Findings Associated With Erythroblastosis Fetalis, West. J. Surg. 59: 192, 1951.

Although innumerable contributions to medical literature concerned with the Rh factor have appeared during the last 10 years, relatively few have dealt with the placental findings. A critical study has been made from the placentas of 845 patients who were found to be Rh negative. Of the Rh-negative group, 88 patients, or 10.4 per cent, developed demonstrable antibodies during their pregnancies. In the group who developed antibodies 44 per cent delivered infants with proved hemolytic disease. The placental findings were correlated with this information.

There is a direct relationship between the fetal blood picture and the finding of increased numbers of nucleated red cells in the fetal vessels of the placenta. Other significant findings which were more or less consistent in the placentas of those babies with proved hemolytic disease were: edema of the stroma, abnormally large villi, a relative decrease in the number of fetal vessels, clubbing of the villi, a persistence of the Langhans' layer, and the presence of Holbauer cells. In those placentas associated with infants who died of hemolytic disease there were 2 or more of these placental abnormalities, while in those infants who had hemolytic disease, but who survived, there was at least 1 of these placental abnormalities. Thus it can be said that the placental evidence is of considerable prognostic significance.

It is of interest to speculate on the actual cause of the placental changes. Are they secondary to changes which are primary with the fetus, or are they a tissue reaction to the circulating antibodies in the maternal blood? It is probable that the placental changes are the direct result of a reaction to the circulating maternal antibodies. WILLIAM BICKERS

Biorn, Carl L., and Davis, Joseph H.: Torsion of the Spermatic Cord in the Newborn, J. A. M. A. 145: 1236, 1951.

It is felt that undiagnosed torsion of the spermatic cord is one common basis for unilateral atrophic testicle so frequently encountered in urologic practice. The authors report two cases which they saw over a period of nine months. The one sign common to both cases was the blue discoloration of the involved testicle that was apparent through the scrotal skin. Scrotal edema over the involved testicle may be apparent. Immediate exploration is the treatment. Exploration and fixation of the opposite testicle are advisable if any question concerning its viability or excess mobility is entertained. WILLIAM BERMAN

Baber, M., Rosser, E., and Lavertine, J.: Carcinoma of the Cervix Uteri in an Infant, Brit. M. J. 1: 392, 1951.

Malignant tumors of the uterus in children are sarcomatous with few exceptions. Confirmed reports of lesions arising from the cervix uteri are usually adenocarcinomas. The authors report a child of 15 months with undoubted cervical carcinoma. The child passed bloody urine and the mother noticed a clot on the vulva. Examination revealed an abdominal mass up to the umbilicus with a normal-appearing vaginal cervix. At laparotomy the mass was found to have originated in the supravaginl cervix, extended up into the corpus, and was firmly adherent to the bladder. No further operation was done. Within weeks the tumor had invaded and ulcerated the vaginal vault and extensive abdominal and liver metastases had occurred. The child died 5 weeks after the exploratory operation

with an immensely enlarged liver (weight 1,550 grams at autopsy) and abdominal carcinomatosis. Pathologists of the Consultant Panel in Morbid Histology of the Pathological Society of Great Britain and Ireland and of the British Empire Cancer Campaign agreed that the tumor was a papillary adenocarcinoma, probably of endocervical origin.

THOMAS L. BALL

Pregnancy, Complications

Ezes, H., and Bourgarel, R.: Are Certain Edemas at the Conclusion of Pregnancy of an Allergenic Nature? Bull. Assoc. d. gynéc. et obst. de langue franç. 2: 241, 1950.

The authors, from Algiers, review the many theories and hypotheses anent the possible etiological factors concerned with the production of edema in pregnant women at the termination of their pregnancies. They favor the allergenic hypothesis because of two facts. First, such patients often give a history of premenstrual edema in their nonpregnant cycle. They accept the explanation of Ales-Sandrini (Rome) that such auto-allergies are induced by a sensitivity of patients to intermediate metabolites of their own estrogens. Second, the authors ran intradermal tests using estradiol on three types of cases: (1) nonpregnant women, (2) normally pregnant women without evidence of edema, and (3) pregnant women with edema at the end of their pregnancies. They obtained no significant reactions in the first two groups but a considerable zone of edema, even superficial necrosis in some, in the last series. Unfortunately, the authors do not state the number of cases or give illustrations or figures.

CLAIR E. FOLSOME

Crichton, Derk: Treatment of the Concealed Accidental Haemorrhage of Pregnancy, Brit. M. J. 1: 401, 1950.

The author compares the various treatments used for concealed accidental hemorrhage of pregnancy at the Peninsula Maternity and Groote Schuur Hospitals, Capetown. For this analysis 120 cases (0.7 per cent of admissions) of the severe form of the condition were used. Multiparas accounted for 90.9 per cent of the cases, while the average age was 35.8 years, parity 5.5, and gravidity 6.3. Albuminuria and/or hypertension were found in 95 per cent of cases. All patients showed degrees of hypotensive shock out of proportion to the revealed blood loss, and almost 80 per cent had a relatively slow pulse rate. The maternal mortality was 10.9 per cent.

In most instances the treatment of shock included heat, morphine, and intravenous glucose-saline solutions. Blood transfusion was not employed per primum. In more recent years the more liberal use of blood has not affected the maternal mortality. As to the various treatments, the investigation showed: (1) rupture of the membranes when contractions supervened, 88 cases (73 per cent) with 7 deaths (8 per cent); (2) rupture of membranes, vulsellum to scalp, and binder, 4 cases without mortality; (3) artificial rupture of membranes in presence of contractions and without preliminary shock therapy, 5 cases with one death; (4) rupture of membranes without contractions present, 23 cases with 5 deaths; (5) cesarean section, 7 cases with 2 deaths.

The author stresses the advisability of treating the shock with crystalloid solutions, and with blood equal to that which has been lost. He feels that there is danger in rupturing the membranes in the absence of contractions, and that vaginal plugging is obsolete. He further states that cesarean section has a small but definite place in treatment; chiefly in those instances where, following conservative measures, the patient's condition deteriorates and there are no uterine contractions. The response to oxytocic drugs and fundal control were often disappointing, but intrauterine packs were not a common necessity. The liberal use of oxygen to maintain high oxygen tension is advised. The author found that renal cortical necrosis was observed in 30 per cent of the necropsies of his series. He advises that the use of oxygen, avoidance of surgery which may cause shock, and care with intravenous therapy will reduce the incidence of anuria.

JOHN T. COLE

Pregnancy, Physiology

Sureau, M., Gounelle, H., and Francois, A.: Modifications of Capillary Fragility at the Time of Delivery, Bull. Assoc. d. gynéc. et obst. de langue franç. 2: 248, 1950.

The authors working at Maternity Hospital de la Pitie, Paris, studied the comparable vascular "resistance" in a series of 113 pregnant women. A pressure cuff, the Lavollay apparatus, was applied to the forearm under a pressure of 40 cm. of mercury for 30 seconds. The number of petechiae were counted. The intensity of reaction was placed arbitrarily into 4 categories: 0, no petechiae; X, 0 to 5 petechiae; XX, 5 to 15 petechiae; and XXX, more than 15 petechiae.

The women were tested at the eighth month of pregnancy, during labor but before delivery, and eight months after delivery. In category 0, at the eighth month of pregnancy, were 29 women (25.6 per cent); in category X 48 women (42.4 per cent); in category XX 17 women (15 per cent); and in category XXX 19 women (16.8 per cent). In category 0, at the time of labor but before delivery, were 15 women .(13.2 per cent); in X 27 women (23.8 per cent); in XX, 42 women (37.1 per cent); and in XXX, 29 women (25.6 per cent). Eight months after delivery the figures show the following categorical distribution: 0, 28 women (24.7 per cent); X, 52 women (46.0 per cent); XX, 19 women (16.8 per cent); and XXX, 14 women (12.3 per cent).

The writers conclude there was a noticeable tendency toward the increase of capillary fragility during labor, and before delivery, which receded rapidly after delivery. They are planning further studies of this phenomenon throughout the duration of pregnancy. Two figures and two tables accompany the article. CLAIR E. FOLSOME

Arnold, Barbara J., Walsh, R. J., and Herzger, Ruth: A Study of the Significance of Rh Antibody Titration During Pregnancy, M. J. Australia, p. 301, Feb. 24, 1951.

The authors feel that in view of the general agreement there is little, if any, correlation between the titer of agglutinins, and the severity of the disease in the fetus. Titration is of no value if the agglutinins have appeared during the current pregnancy. It is impossible from the results of titration to predict an Rh-negative child with certainty. A rise or fall in titer is nearly always associated with an Rh-positive fetus who suffered from hemolytic disease of the newborn, but the majority of affected infants produced no change in the maternal agglutinins. WILLIAM BERMAN

Merivale, W. H. H., and Richardson, G. O.: Changes in Size of Red Cells During Normal Pregnancy, Brit. M. J. 1: 463, 1950.

The purpose of this paper is to investigate the possibility that women called on to provide extra antianemic factor during pregnancy might show a relative deficiency, producing measurable changes in the size or other features of the erythrocytes. Sixteen healthy pregnant women were studied at various stages of pregnancy. The red cell counts remained normal, and there were no significant differences in mean corpuscular volume or in mean corpuscular diameter. The latter, however, showed statistically important variations from month to month. Thus the mean corpuscular diameter varies over a much wider range than in a nonpregnant individual. The authors feel that there is a definite tendency to increased anisocytosis in pregnancy even though the hemoglobin, red cell count, and mean corpuscular volume are normal. JOHN T. COLE

Dunsford, I.: Agglutinin Anti-P in Pregnancy, Brit. M. J. 1: 15, 1949.

There are a few references in the literature to immune or naturally occurring anti-P. During routine investigations at the National Blood Transfusion Service, Sheffield, the agglutinin anti-P was discovered in the sera of two pregnant women. These two cases are described in detail; both women bore normal infants. The investigations carried out suggest

that anti-P agglutinins were of natural occurrence and may be compared to naturally occurring agglutinins anti-A and anti-B. It would also appear from the two cases that anti-P is unlikely to be a causative agent in hemolytic diseases of the newborn. JOHN T. COLE

Pregnancy, Toxemia

Moore, Henry, Jessop, W. J. E., O'Donovan, D. K., Barry, A. P., Quinn, Brigid, and Drury, M. J.: Cortisone in the Treatment of Toxemia of Pregnancy, Brit. M. J. 1: 841, 1951.

Considering that toxemias of pregnancy may in part at least be explained on the hypothesis that they are manifestations of Selye's general stress adaptation syndrome and the scattered evidence of alteration in adrenal gland activity in normal and toxemic pregnancy, the authors have reported the findings in 8 cases treated with cortisone. The authors state they approached the study with certain reservations but certain reports in the literature of the effect on patients with acute nephritis and nephrosis prompted more optimism toward the proposed study. All cases were initially treated with salt restriction, bed rest, and sedation. Details were recorded on fluid exchange, weight, blood pressure, albuminuria, edema, eosinophil counts, and blood chemistry findings.

The cases are described in detail. The authors state emphatically that no definite conclusions can be drawn regarding the effect of cortisone in these cases but it appears to have had a beneficial effect. They feel that routine sedation is essential initially but can be reduced after the treatment is started. Cortisone appears to prolong the period of gestation in patients who would ordinarily require termination of the pregnancy earlier.

The patient's subjective symptoms and her sense of well-being showed marked improvement; however, effect on blood pressure was disappointing. Some patients developed ascites.

The results obtained showed five patients discharged well; one developed schizophrenia, one underwent extensive cardiovascular-renal investigation and one died of congestive heart failure. Seven babies were born alive of whom two subsequently died (prematurity and intracranial hemorrhage). The eighth baby was stillborn, death attributed to subtentorial hemorrhage. DONALD G. JOHNSON

De Giorgi, Luigi: Pathological Findings in the Hypophysis in Abruptio Placentae, Arch. ostet. e ginec. 55: 311, July-Aug., 1950.

The author has studied the histologic findings in the hypophysis in four cases of abruptio placentae. The main changes were found in the anterior lobe and consisted of localized or diffuse inflammatory infiltration, mostly perivascular, of lymphocytes only. This pathological change is identical with that found in eclampsia and brings us to consider the relation between toxemia and abruptio placentae.

RINA D'AMICO

Timonen, S., and Schroderus, K. A.: The Effect of Papaverine on the Circulation of Pre-eclamptic and Eclamptic Patients, Acta obst. et gynec. Scandinav. 29: 377, 1950.

Since it is recognized that vasospasm constitutes an important feature of toxemia of pregnancy, the use of spasmolytic drugs has been suggested for the treatment of the acute pre-eclampsia-eclampsia syndrome. The effect of intramuscular injections of papaverine hydrochloride on the blood pressure and cardiac output of forty patients with acute pregnancy toxemia was studied. The drug consistently produced a prompt decrease in systolic pressure and a delayed drop in diastolic pressure, thus bringing about a fall in pulse pressure. There was regular slowing of the pulse, and concomitant temporary reduction in cardiac output, ultimately compensated by decrease in diastolic blood pressure level. In view of the fact that the tissues of toxemic patients are relatively anoxic as a result of generalized vasospasm, any decrease in cardiac output would seem to be unde-

sirable, especially in the presence of a narrowed pulse pressure. Papaverine produces reduction in cardiac output by causing vasodilation of the coronary artery system, thus directly inhibiting myocardial activity. In the series studied, several patients showed a steady decline in general condition following administration of papaverine. The conclusion is drawn that the slight improvement obtained in some of the patients was more than offset by the disadvantages of the drug, and its use in acute pregnancy toxemias is not recommended.

DOUGLAS M. HAYNES

Bromberg, Y. M., and Toaff, R.: Habitual Foetal Death Associated With Recurrent Toxemia of Pregnancy in Diabetic Patients, J. Obst. & Gynaec. Brit. Emp. **57**: 240, 1950.

Drs. Bromberg and Toaff report a study of 2 diabetic women, in whom diabetes was of long standing, eighteen years in one case and ten years in the other; in the first case, in which the diabetes was well controlled, 3 successive pregnancies terminated in toxemia and fetal death; and in the second case, in which the diabetes was mild, 2 successive pregnancies ended in the same way. In both cases the chief symptoms of toxemia were water retention with excessive gain in weight, generalized edema, and edema of the ocular fundi. Other symptoms of toxemia, such as hypertension and albuminuria, were mild. Intrauterine fetal death occurred about one week after the onset of symptoms of water retention and was followed by profuse diuresis and the early clearing up of the other toxic symptoms. In each case a macerated, hydropic fetus and an edematous placenta were delivered. In only one pregnancy was there evidence of hormonal imbalance, and treatment with estrogens and progesterone did not alter the course of the case. In diabetes of long standing, some degree of vascular damage occurs and was manifested in these two patients by hemorrhagic retinopathy. Both the recurrent toxemia and the fetal deaths in these 2 cases are explained as due to this general vascular damage plus that which is brought on by the pregnancy impairing the blood supply to the uterus and its contents, resulting in disturbance in water metabolism affecting the mother, the fetus, and the placenta.

HARVEY B. MATTHEWS

Kenny, R. A., Lawrence, R. F., and Miller, D. H.: Haemodynamic Changes in the Kidney in "Toxemia of Late Pregnancy," J. Obst. & Gynaec. Brit. Emp. **57**: 17, 1950.

A study of renal hemodynamic conditions in 4 normal pregnant women, and 20 women with toxemia of late pregnancy, by means of the inulin-Diodone clearance tests and Lamport's formula for calculating arteriolar resistance is presented. It was found that in normal pregnancy there are only minor alterations in hemodynamic equilibrium of the kidneys. The rate of renal plasma flow is slightly increased, but the glomerular filtration rate is normal. The resistance of the afferent glomerular arteriole is raised only slightly and the glomerular pressure slightly reduced. In toxemic subjects the renal plasma flow and glomerular filtration are both reduced. There is a definite increase in the resistance of the afferent glomerular arteriole, that is, a constriction of the afferent arteriole, and a definite reduction of the glomerular pressure. In some cases, there was some efferent arteriolar constriction, which appeared to be a compensatory mechanism, tending to increase the glomerular pressure somewhat. In many of the cases of toxemia the total arteriolar resistance was increased, but this showed no direct relationship to the systemic blood pressure. The authors consider that this indicates that hypertension in the toxemia of pregnancy is not due primarily to increased renal resistance. These findings, therefore, support the theory that the basic pathology of the late toxemia of pregnancy is a generalized arterial hypertension which results in altered functions of certain organs which produce the characteristic clinical picture.

HARVEY B. MATTHEWS

Browne, O'Donel: The Treatment of Eclampsia, J. Obst. & Gynaec. Brit. Emp. 57: 573, 1950.

This is a preliminary report on the present treatment of eclampsia at the Rotunda Hospital of Dublin by the use of intravenous drip of sodium thiopentone in 10 per cent dextrose solution (3 Gm. thiopentone per 1 liter of dextrose solution). Before the intravenous drip apparatus has been set up 0.5 Gm. sodium thiopentone in 10 ml. distilled water is given intravenously to prevent the occurrence of eclamptic convulsions. Morphine is not used. If morphine has been given this initial dose of thiopentone is reduced one-half. Omitting the use of morphine diminishes respiratory depression, but, if any such depression occurs, continuous oxygen is given until the patient's color becomes and remains satisfactory. The use of dextrose without saline and restriction of fluid intake promote diuresis and reduce edema. Under the sodium thiopentone therapy the patient should sleep quietly. If necessary to maintain quiet sleep additional sodium thiopentone solution (0.5 Gm. in 10 ml. sterile water) may be injected into the drip tube (2 ml. at a time as necessary). The patient is kept asleep for at least twenty-four hours and longer if necessary by receiving from 3.27 to 7.5 Gm. of sodium thiopentone. Recovery of conciousness is slow after the thiopentone drip is stopped, but no case of residual mental confusion or other mental disturbance has been observed. Fluids are not given by mouth until satisfactory diuresis is established and a satisfactory bowel action has been produced, after which intravenous fluids are no longer necessary. In 15 patients with eclampsia treated before the thiopentone-dextrose therapy was adopted, in which morphine, magnesium sulfate, and glucose-saline were employed, there were 3 maternal deaths, one stillbirth, and 2 neonatal deaths. In the 18 cases treated by the thiopentone-dextrose method, there was only one maternal death and no neonatal deaths, but there were 5 stillbirths, 3 of which were due to placental degeneration and accidental hemorrhage. In the other 2 cases death may have been due to intrauterine asphyxia, but there was no proof that such was the case. The maternal mortality rates for the two series were 12.12 per cent and 5.5 per cent, respectively, thus showing the apparent efficacy of the new therapy, particularly in controlling convulsions. The author hopes that other centers will give this regime a thorough trial and report their results.

HARVEY B. MATTHEWS.

Dougray, T.: Antihistamines in the Treatment of Nausea and Vomiting of Pregnancy, Brit. M. J. 2: 1081, 1949.

The author briefly reviews some current concepts of etiology of vomiting of pregnancy. The clinical study involved 94 patients treated with antihistamine drugs with 78 patients cured, 4 improved, and 12 failures. No untoward effects except drowsiness were noted. This effect was easily counteracted by 5 mg. of amphetamine sulfate. DONALD G. JOHNSON

Editorial: Cortisone and Toxaemia of Pregnancy, Brit. M. J., April 21, 1951.

The editorial refers to the article by Prof. Henry Moore and his colleagues in Dublin and reported in the April 21, 1951, issue of the *British Medical Journal.*

It is pointed out that the beneficial effects of cortisone were produced without any significant change in the disease process. He suggests that in spite of this fact cortisone may afford protection for the patient until the process naturally resolves. DONALD G. JOHNSON

Dieckmann, William J., Smitter, Robert C., and Pottinger, Russell E.: Liver Function Studies in Normal and Toxemic Pregnancy, Surg., Gynec. & Obst. 92: 598, 1951.

In the study of 85 patients with normal pregnancies, 44 with pre-eclampsia and 23 with chronic hypertensive vascular disease, Dieckmann and co-workers were unable to find any

difference in liver function as tested by thymol turbidity, cephalin flocculation, serum bilirubin, and urine bilirubin tests. The authors felt that the cephalin flocculation might possibly indicate, early in pregnancy, those patients who were later destined to develop pre-eclampsia.

LOUIS M. HELLMAN

Cartwright, E. W.: Dramamine in Nausea and Vomiting of Pregnancy, West. J. Surg. **59:** 216, 1951.

In 38 patients with moderate to severe vomiting in pregnancy there was an estimated 50 per cent relief of nausea and vomiting in 59 per cent of the patients treated. Sixteen of the patients in this group enjoyed relief at what was estimated to be 24 per cent. Degree of drug effectiveness was determined percentagewise. In the group 38 patients received a placebo and those who obtained 50 per cent relief or better numbered 18, or 47.4 per cent of the series. This compares with 59 per cent who received a similar degree of relief following the use of Dramamine. The most effective dose employed by the author was 100 mg. of the drug administered twice daily. When Dramamine was given in large doses the incidence of side reactions such as dizziness and sleepiness was increased. The author concludes that factors other than clinical and physiological ones play a part in the degree of clinical relief following the use of any medication in patients with hyperemesis gravidarum. The abstracter concludes after careful study of this lengthy report that Dramamine offers little advantage over a sugar pill in the treatment of this clinical syndrome.

A discusser of the paper reports his observations upon gastric motility obtained by placing balloons in the stomachs of young women. He concludes that by power of suggestion alone the stomach can be made to do most anything the experimenter desires. It can be made to react in hyperactive fashion. All motility can be suppressed and these physiological changes can be induced solely by suggestion on the part of the investigator. With the stomach so readily influenced by suggestion it becomes apparent how difficult it is to evaluate drug therapy.

WILLIAM BICKERS

Erratum

In the article by Barfield, Harrod, and Greenblatt entitled "Transmucosal Administration of Methyl Testosterone, Free Testosterone, and Testosterone Propionate," which appeared on page 1354 of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, June, 1951, the footnote to the article should be corrected to read:

Acknowledgment is made to the following pharmaceutical houses which cooperated in this study:

Chemical Specialties, Inc., Syntex, S.A.—free testosterone and methyltestosterone tablets for buccal absorption.
Wyeth, Inc.—free testosterone—"Membrettes."
Schering Corporation—testosterone propionate—Oreton Buccal Tablets.
Ciba Pharmaceutical Products, Inc.—methyltestosterone—Metandren Linguets.

Correspondence

Superfetation

To the Editor:

Dr. Gaupin has submitted a case of superfetation to the JOURNAL (AM. J. OBST. & GYNEC. 62: 212, 1951).

There does not appear to be any evidence that this represents "superfetation." May I suggest the more obvious and probable, that this represents a twin gestation, and that the disparity in size of the aborted specimens may be explained on the basis of variance in maternal-fetal circulation, or perhaps earlier death of the smaller specimen.

There have been many twins born at or near term showing very similar weight and size differential. It does not appear that such evidence as this or that presented by Dr. Gaupin may be accepted as proof of superfetation.

SIDNEY C. REICHMAN, M.D.

NASHVILLE, TENN.
AUG. 2, 1951

Reply by Dr. Gaupin

To the Editor:

In reply to Dr. Sidney C. Reichman's letter, I would like to state the following:

There was an error in printing on the closing line of my report. "Presented for delivery" should have read "Presented for your consideration."

While superfetation is of rare occurrence, there has been a sufficient number of case reports in the literature to justify the belief that it does occur.

Since ovulation is an essential factor in superfetation, Ravano, in 1907, reported his findings in 100 abdominal operations on pregnant women. He stated 5 per cent showed recent rupture of a corpus luteum.

Drs. Murless and McLaughlin in 1937[1] reported a case of "Fertilization at the Third Month of Uterine Pregnancy." They also state that pregnancy does not completely fill the uterine cavity until after the third month. This would allow an ovum to gravitate to the lower uterine segment and there become impregnated.

The corpus luteum wanes about the third month of pregnancy, so that ovulation could occur at this time. This corresponds to the time this patient again became pregnant.

The second fertilization was apparently in the lower uterine segment (see findings of vaginal examination in the case report), and was probably the cause of the abortion. That this view is correct was substantiated by the fact that the small fetus presented for delivery before the larger one.

That superfetation was considered was based on the following:

1. That ovulation can and does occasionally occur, after pregnancy has already existed.
2. The rather marked disparity in the size of the two fetuses.
3. The perfect state of preservation of the 6 weeks fetus. Had it expired at the sixth week of gestation, liquefaction changes would probably have taken place.
4. The low uterine implantation of the second fertilization was the likely cause of the abortion.

C. E. GAUPIN, M.D.

LOUISVILLE, KY.
SEPT. 15, 1951

Reference

1. Murless, Bryan C., and McLaughlin, F. M.: Brit. M. J. 1: 1309, 1937.

Items

The American Academy of Obstetrics and Gynecology

The National Federation of Obstetric-Gynecologic Societies has reconstituted itself as The American Academy of Obstetrics and Gynecology. This action was taken at the Federation meeting held on June 13, 1951, in Atlantic City, in response to the long-felt need for a national society for obstetricians and gynecologists based on individual and personal membership.

The following officers were elected at this meeting:

President—Woodard D. Beacham, New Orleans, La.
President-Elect—Carl P. Huber, Indianapolis, Ind.
Vice-President—Louis H. Douglass, Baltimore, Md.
Treasurer—Herbert E. Schmitz, Chicago, Ill.
Secretary—Ralph A. Reis, Chicago, Ill.
Executive Board—Robert G. Craig, San Francisco, Calif.
John L. Parks, Washington, D. C.
Charles D. Kimball, Seattle, Wash.
Samuel B. Kirkwood, Winchester, Mass.
Philip F. Williams, Philadelphia, Pa.

The Academy was incorporated on Aug. 4, 1951, as a nonprofit corporation under the laws of the State of Illinois. Its objects are listed in the Constitution and By-Laws which were adopted at a meeting held at Hot Springs, Va., on Sept. 5, 1951. They include "fostering and stimulating interest in obstetrics and gynecology and all aspects of the work for the welfare of women which properly come within the scope of obstetrics and gynecology."

The first business meeting of the Academy will be held at the time of the meeting of the American Congress on Obstetrics and Gynecology in Cincinnati, March 31 through April 4, 1952. The First Annual Clinical Meeting will be held in Chicago, Ill., during the winter of 1952-1953.

Applications for Fellowship may be obtained from the Secretary's office, 116 South Michigan Avenue, Chicago 3, Ill.

RALPH A. REIS, M.D.
Secretary

Urology Award

The American Urological Association offers an annual award of $1,000.00 (first prize of $500.00, second prize $300.00, and third prize $200.00) for essays on the result of some clinical or laboratory research in urology. Competition shall be limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Chalfonte-Haddon Hall, Atlantic City, N. J., June 23-26, 1952.

For full particulars write the Secretary, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, N. J. Essays must be in his hands before February 15, 1952.